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Supreme Court, U.S.
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No. 90-

IN THE

Supreme Court of the United States

OCTOBER TERM, 1990

ABBOTT LABORATORIES,
Petitioner,

v.

DR. FRANK D. YOUNG, COMMISSIONER,
Respondent.

Petition for Writ of Certiorari to the United States Court of Appeals for the District of Columbia Circuit

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PETITION FOR WRIT OF CERTIORARI

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QUESTIONS PRESENTED

The 1984 "Hatch-Waxman" Amendments to the Federal Food, Drug, and Cosmetic Act established streamlined procedures for approval of generic copies of branded drug products already on the market. As an incentive to research and development, the statute also provided that no such copy would be approved for sale prior to the expiration of one of five mutually-exclusive periods of "market exclusivity," ranging in length from two to ten years depending upon the product involved and its relationship to previously approved products. A majority of the court of appeals, in direct conflict with the judgment of the United States Court of Appeals for the Federal Circuit, purported to find the criteria defining the market exclusivity periods ambiguous, and directed Respondent Commissioner of Food and Drugs to construe the statute so as to accord Petitioner's prescription anticonvulsant DEPAKOTE only two years' exclusivity, not the ten years' to which Petitioner believed the drug was entitled.

The questions presented are:

1. Whether the court of appeals, on specious grounds of ambiguity and because of an express disagreement with the policies advanced by the statute's plain language, wrongly refused to implement the clear and unambiguous market exclusivity provisions as written by Congress?

2. Whether the court of appeals, by refusing to implement clear statutory language because the applicable legislative history did not affirmatively support the plain-language construction, wrongly denied the market exclusivity provisions the presumption of legislative validity to which they were entitled?

PARTIES AND RULE 29.1 STATEMENT

In addition to the parties named in the caption, Par Pharmaceuticals, Inc. entered an appearance as an *amicus curiae* in the court of appeals. Petitioner has no parent company and no subsidiaries other than wholly-owned subsidiaries.

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PETITION FOR WRIT OF CERTIORARI

Petitioner Abbott Laboratories respectfully prays that a writ of certiorari issue to review the judgment of the United States Court of Appeals for the District of Columbia Circuit in this case.

OPINIONS BELOW

The Opinion of the United States Court of Appeals for the District of Columbia Circuit is reported at 920 F.2d 984 (D.C. Cir. 1990) and is reprinted as Appendix A, *infra*, 1a-24a. Rehearing was denied without opinion. Appendix C, *infra*, 100a-101a.

The Memorandum and Order of the United States District Court for the District of Columbia is reported at 691 F. Supp. 462 (D.D.C. 1988) and is reprinted as Appendix B, *infra*, 38a-61a. The court's Memorandum

and Order disposing of post-judgment motions is unpublished, and reprinted at App. 25a-37a.

JURISDICTION

The United States Court of Appeals for the District of Columbia Circuit entered its judgment on December 7, 1990. App., *infra*, 1a. A Petition for Rehearing and Suggestion of Rehearing *En Banc* was denied by Order entered on March 14, 1991. App. C, *infra*, 100a-101a.

The jurisdiction of this Court to review the judgment of the District of Columbia Circuit is invoked under 28 U.S.C. 1254(1).

STATUTES

The Federal Food, Drug, and Cosmetic Act, as amended by the Drug Price Competition and Patent Term Restoration Act, P.L. No. 98-417, Sections 505(c)(3)(D)(i)-(v), 505(j)(4)(D)(i)-(v), and 201(a), 21 U.S.C. §§ 355(c)(3)(D)(i)-(v) and 355(j)(4)(D)(i)-(v), and 35 U.S.C. § 156(f), are set forth at Appendix D, *infra*, 102a-109a.

STATEMENT

This case involves the statutory scheme created by Congress in 1984 to facilitate approval of generic copies of branded drugs, and to enhance incentives for research and development that bring new drugs to market. At issue are the statutory criteria for determining a new drug's "market exclusivity" period—the period of time that must pass after the drug is approved for sale before a generic copy of that drug may also be sold.

The 1984 legislation—the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (hereinafter the "Hatch-Waxman Amendments")—fundamentally altered the process by which pharmaceuticals are brought to market, and struck a precise balance between what Congress considered to be potentially competing and vital public interests. That

balance is manifested no more clearly than in the various market exclusivity provisions, whose meaning has been placed in dispute by the erroneous split decision of the court of appeals in this case. Review by this Court is necessary to settle the important question of the meaning of the market exclusivity provisions, and resolve a conflict between the court of appeals below and the Federal Circuit, which construed essentially identical language differently in connection with the 1984 legislation's patent term extension provisions.

Review is also necessary because the appellate court's decision dramatically expands the scope of judicial review of statutory language. Out of misplaced concern over the wisdom of congressional policy, the majority of the court of appeals declared to be ambiguous a portion of the statutory language that simply could not be clearer—as Petitioner, Respondent, agency counsel from the Department of Justice and three federal courts had unanimously theretofore agreed. Moreover, although it found no affirmative evidence that the concededly "more obvious" construction urged by Petitioner was irrational or contrary to legislative intent, the majority refused to implement it, instead remanding the matter in order for Respondent to rubber-stamp the contrary construction that the majority speculates Congress "seems to have had [in mind]." This judicial adventurism in the face of an unambiguous statutory mandate is contrary to settled principles of judicial review, and upsets the constitutional roles of Congress and the federal courts.

A. DEPAKOTE

The drug at issue in this case is a prescription anticonvulsant marketed by Abbott under the trade name DEPAKOTE. DEPAKOTE is indicated for use as sole and adjunctive therapy for patients, including epileptics, who experience various types or combinations of seizures.

R. 3-4.[1] It is administered orally, in enteric-coated tablet form, and is typically prescribed on a long-term—even lifetime—basis to reduce the frequency and severity of seizures. R. 92-93. For many patients DEPAKOTE may control seizures completely, allowing such patients to be gainfully employed, obtain driver's licenses, and in other ways live more normal lives.

This case involves the application to DEPAKOTE of two terms of art in food and drug law whose meaning is not in dispute. The first is the familiar term "active ingredient," which appears repeatedly in the text of the market exclusivity provisions, and which refers to a drug's final dosage form *prior* to administration to a patient. R. 30. The second term is "active moiety," which nowhere appears in the statute, and which refers to the drug's pharmacologically active components in the body *after* administration. *Ibid.* A drug's active ingredient frequently is different from its active moiety. DEPAKOTE's active ingredient, for example, is divalproex sodium. R. 296. After administration to the patient, however, divalproex sodium reacts with water in the patient's digestive tract to form a different chemical entity, valproic acid, which provides the drug's therapeutic effect. R. 955-56. DEPAKOTE'S active moiety is thus valproic acid. R. 27.

Abbott also markets DEPAKENE, as an anticonvulsant product with valproic acid as both its active ingredient and its active moiety. DEPAKENE was approved in 1978. R. 251-53. However, when valproic acid is administered directly, as in DEPAKENE, it can cause significant gastrointestinal side effects. R. 260. DEPAKOTE, with its different active ingredient, is able to deliver a therapeutic dose of medication while substantially reducing these problems. R. 92.

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[1] As used in this Petition, "R. ——" refers to the administrative record in this case as compiled by Respondent.

Abbott filed a new drug application ("NDA") for DEPAKOTE on December 29, 1981. R. 310. The NDA was approved March 10, 1983. R. 296. Until DEPAKOTE, Respondent had never approved a product having divalproex sodium as its active ingredient. *E.g.*, App., *infra*, 4a-5a.

B. The Statutory Scheme And The Market Exclusivity Provisions

On September 24, 1984, the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-392 (hereinafter "the Act"), was amended by passage of the Hatch-Waxman Amendments. The Hatch-Waxman Amendments had two purposes. First, they simplified the process for approving generic copies of branded drugs by freeing a would-be manufacturer from conducting expensive and time consuming safety and efficacy studies. Instead, the statute created two mechanisms for bringing a generic to market: The abbreviated new drug application ("ANDA"), pursuant to which a manufacturer could rely upon studies performed by the party who originally developed the product, and the "paper NDA," which could be based upon data in the scientific literature. *See* Sections 505(b)(2), (j) of the Act, 21 U.S.C. §§ 355 (b)(2), (j).

Second, Congress recognized that the companies whose efforts brought the new pharmaceuticals to market had legitimate commercial interests, and that preserving these interests was essential to enhancing the incentives for continuing research and development efforts. *See* H.R. Rep. No. 857, 98th Cong., 2d Sess., pt. 1, at 14-15, *reprinted in* 1984 U.S. Code Cong. & Admin. News 2647, 2647-48. The balance between these potentially conflicting interests was struck in the creation of five mutually exclusive periods of "market exclusivity," ranging in duration from two years to ten years, during which neither ANDAs nor "paper" NDAs could be

approved and made effective.[2] The five periods are established by each of sections 505(c)(3)(D)(i)-(v) and 505(j)(4)(D)(i)-(v) of the Act as amended by Hatch-Waxman Amendments, with the former sections limiting approval of "paper" NDAs and the latter, ANDAs.

Two of the five categories are directly at issue here. Under section 505(j)(4)(D)(i),[3] certain products whose NDAs were approved for sale in a statutorily-prescribed period between January 1, 1982 and September 24, 1984 (the effective date of the Hatch-Waxman Amendments) are entitled to ten-years' market exclusivity, measured from the date of such approvals. Under section 505(j)(4)(D)(v), however, other products whose NDAs were approved during the same period obtain only two-years' market exclusivity, measured from September 24, 1984.

The text established by Congress for determining whether the ten-year or the two-year period of exclusivity applies to a particular drug product approved during the statutory period is straightforward and unambiguous. If the product contains no "active ingredient (including any ester or salt of the active ingredient)" previously approved by Respondent, the ten-year market exclusivity provision applies.[4] Section 505(j)(4)(D)(i).

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[2] "Market exclusivity" thus is different from a patent right: While a patent owner can exclude all others from competing with like products, market exclusivity only delays approval of ANDAs or "paper" NDAs. A second company that obtains NDA approval for an existing product is free to compete even during the "exclusivity" period.

[3] The relevant language defining the period of market exclusivity for a particular product is the same for both ANDAs and "paper" NDAs. For clarity, only the statutory counterpart relating to ANDAs will be cited hereinafter.

[4] "Esters" and "salts" are specific chemical variations of underlying chemical entities. Their definitions are not in dispute in this case. Indeed, no disputed technical issues of any kind are presented here.

If the product does contain "an active ingredient (including any ester or salt of the active ingredient)" that has been previously approved, only two-years' exclusivity is due. Section 505(j)(4)(D)(v). It is undisputed that neither the active ingredient of DEPAKOTE, divalproex sodium, nor an ester or salt of divalproex sodium, had been approved by Respondent prior to the approval of DEPAKOTE. For this reason, DEPAKOTE is entitled to ten-years' exclusivity.

The same statutory test is the key to application of market exclusivity periods for drugs that have been or will be approved after the effective date of the Hatch-Waxman Amendments. Where such a drug's "active ingredient (including any ester or salt of the active ingredient)" has not previously been approved, five years' market exclusivity attaches. Section 505(j)(4)(D)(ii). There is no market exclusivity otherwise, unless new clinical studies were performed, in which case a three-year period attaches. Section (j)(4)(D)(iii).[5] All of the market exclusivity periods are self-effectuating: The statute provides no administrative mechanism for determing which period applies to a given drug, or for appealing decisions deemed to be incorrect.

C. Abbott's Efforts To Obtain Ten-Years' Exclusivity For DEPAKOTE

Following passage of the Hatch-Waxman Amendments, Abbott submitted information to Respondent identifying the active ingredient of DEPAKOTE (divalproex sodium), providing required approval and marketing information, and stating that the drug was entitled to ten-years' exclusivity, to and including March 10, 1993. R. 19-20. Without prior notice or an opportunity for Abbott

[5] The fifth market exclusivity provision also accords three years' exclusivity to any supplement to an approved drug based upon new clinical testing. Section 505(j)(4)(D)(iv).

to comment, and accompanied by no explanation of any kind, Respondent announced that DEPAKOTE was entitled only to two-years' market exclusivity under section 505(j)(4)(D)(v) of the Act, to and including September 24, 1986. This decision appeared as one of hundreds published by Respondent in the Sixth Edition of *Approved Prescription Drug Products* (September 1985). Complaint, Exh. B. Petitioner objected, and by letter dated August 12, 1986, an official from Respondents' Bureau of Drugs and Biologics dismissed Petitioner's objections and purported to justify the classification. R. 27-28.

On August 29, 1986 Petitioner submitted a Citizen Petition to Respondent pursuant to 21 C.F.R. § 10.30 requesting that DEPAKOTE be accorded the full ten-year exclusivity period to which it is due in accordance with the plain language of the Hatch-Waxman Amendments. R. 1. Petitioner also filed a Request for Stay, requesting that no ANDAs or "paper" NDAs be granted for products containing divalproex sodium until resolution of Petitioner's Citizen Petition. R. 66.

Respondent denied Petitioner's petitions on February 11, 1988, almost eighteen months after they were filed. *See* Docket No. 86P-0367, App., *infra*, 62a-91a. Respondent dismissed the explanation previously offered by its Bureau of Drugs and Biologics and instead purported to justify its decision on three alternative and inconsistent constructions of the market exclusivity provisions: 1) That the term "active ingredient" should simply be read to mean "active moiety" in the market exclusivity context, but nowhere else in the Hatch-Waxman Amendments or the Act. App., *infra*, 82a-83a; 2) That the entire *phrase*, "active ingredient (including any ester or salt of the active ingredient)," actually means "active moiety" App., *infra*, 83a; and 3) That the express statutory criteria for market exclusivity actually constitute a grant of authority to extend the longer period of exclusivity to drugs that, in Respondent's sole discretion, represent "substan-

tial investments in research and development [or] significant therapeutic innovations." App., *infra*, 80a.

The effect of substituting "active moiety" for the proper statutory test would be to deny ten-years' exclusivity to DEPAKOTE. Although neither its active ingredient nor an ester or salt of its active ingredient had previously been approved for sale (the statutory test), DEPAKOTE's active moiety, valproic acid, had been approved previously in DEPAKENE. That observation, and the fact that Petitioner as a consequence was not required by Respondent to perform safety and efficacy testing for the DEPAKOTE NDA, also were the sole grounds on which Respondent concluded that DEPAKOTE did not meet the supposed, non-statutory requirement that a drug represent a "substantial" investment or a "significant" innovation.

Respondent's February 11, 1988 decisions constituted final agency action. With its administrative remedies exhausted, Petitioner filed this suit on February 23, 1988, maintaining that denial of its Citizen Petition and Request For Stay was arbitrary and capricious, not in accordance with law, and short of statutory right, all in violation of the Administrative Procedure Act (5 U.S.C. §§ 701-706) and the Hatch-Waxman Amendments.

D. Proceedings Below

1. *Proceedings in The District Court*

The litigation proved to have a troubled course through the district court. In the first stage, the parties filed cross-motions for summary judgment.[6] Petitioner argued that Respondent was required to apply the clear and unambiguous statutory test pursuant to which DEPAKOTE was

[6] Under Petitioner's interpretation of the Hatch-Waxman Amendments there were no scientific facts in dispute, and for purposes of its motion conceded various scientific issues raised by Respondent.

entitled to ten-years' market exclusivity. Respondent, abandoning the argument that an allowance of ten-years' exclusivity was a matter left to agency discretion, pursued the notion that the test should be whether a drug possessed a new "active moiety," despite Congress' use of precise terms—"active ingredient," "salt," and "ester"—having a different meaning. App., *infra*, 50a.

The District Court denied Petitioner's motion and granted summary judgment in favor of Respondent on July 25, 1988. App., *infra*, 38a, 61a. In so doing, however, the court accepted Petitioner's fundamental argument that the ten-year exclusivity provision applies to DEPAKOTE. Specifically, the District Court ruled that the "plain language" of the ten-year exclusivity provision was unambiguous, and allowed no other interpretation than that put forth by Petitioner. *See id.* at 55 n.9. For reasons that remain unclear, however, the District Court did not apply the same reasoning to the identically-worded two-year exclusivity provision. Adopting a construction never advanced by Respondent, the district court found that DEPAKOTE was governed by both the ten-year and the two-year provisions, creating an "irreconcilable statutory conflict" that the court then resolved against Petitioner. *Id.* at 56a-57a.

Although Respondent prevailed on summary judgment, it was sufficiently alarmed by the District Court's decision to initiate a second phase of litigation by filing a "Motion To Alter Memorandum." The focus of the motion was the District Court's conclusion that Respondent could not maintain one interpretation of the term "active ingredient" for market exclusivity purposes and another interpretation for all other purposes under the Act. Respondent incorrectly denied it had urged inconsistent interpretations, and argued only that the *phrase* "active ingredient (including any ester or salt of the active ingredient)" actually means "active moiety." Respondent advanced five arguments in support of its motion, including a re-

newed plea that its own policy preferences be rubber-stamped under the guise of deference.

The District Court denied Respondent's motion on June 22, 1989, finding that the agency had merely repeated arguments already raised and considered on summary judgment, and at the same time denied a request by Petitioner to be provided with advance notice of any approvals of generic copies of DEPAKOTE in order that it might have the opportunity to seek equitable relief.[7] App., *infra*, 36a. The district court did not hold, conclude, or even suggest that the phrase "active ingredient (including any ester or salt of the active ingredient)" could be equated with "active moiety," as Respondent maintained.

2. *Proceedings in The Court of Appeals*

Petitioner appealed. During briefing in the court of appeals, a panel of the United States Court of Appeals for the Federal Circuit issued a unanimous decision construing virtually identical statutory language in the patent-term extension provisions of the Hatch-Waxman Amendments.[8] *See Glaxo Operations UK Ltd.* v. *Quigg*, 894 F.2d 392 (Fed. Cir. 1990). That court, affirming the U.S. District Court for the Eastern District of Virginia, held that the statutory language was clear, precise, and

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[7] There remains no bar to approval of generic copies of DEPAKOTE, and Par Pharmaceuticals, Inc., which filed a brief as an *amicus curiae* in an early stage of proceedings in the court of appeals, disclosed that it had an ANDA for divalproex sodium pending before Respondent. To date, however, no generic copies of DEPAKOTE have been approved. The ten-year exclusivity Petitioner seeks for DEPAKOTE would run through March 10, 1993.

[8] Title I of the Hatch-Waxman Amendments provides for an extension of the terms of certain patented drug products to compensate manufacturers for regulatory delays. Pub. L. No. 98-417, Title I, 98 Stat. 1585 (1984). The issue in *Glaxo* turned on the meaning of the term "drug product," defined by the statute to be "the active ingredient of a new drug, . . . including any salt or ester of the active ingredient . . . ." 35 U.S.C. § 156(f)(2).

unambiguous, and had the plain meaning ascribed to it by Petitioner in this case.[9] The court rejected the contention that the language should be read to mean "active moiety," observing that the statute utilized familiar terms —"active ingredient," "salt," and "ester"—that were well-defined at the time of its passage and finding no basis in the legislative history or elsewhere to conclude that it served an irrational purpose. *Id.* at 396-97.

Nevertheless, on December 7, 1990, a divided panel of the United States Court of Appeals for the District of Columbia Circuit rejected the constructions of the statute advanced by Petitioner (as well as the Federal Circuit), Respondent, and the District Court, and announced it had found an ambiguity in the statutory language that had theretofore escaped the notice of all courts and parties. The majority declared that the word "the" in the key statutory phrase, "active ingredient (including any ester or salt of *the* active ingredient," was ambiguous. Although as a matter of grammar both references to "active ingredient" must be to the same entity, the majority speculated that the second use of the term might somehow refer to any and all active ingredients that Respondent had *ever* approved, a construction that would deny ten-years' exclusivity to DEPAKOTE. App., *infra*, 7a-8a. Finding the statute capable of two interpretations, the majority proceeded to reject the plain meaning construction outright and to direct that the matter be returned to Respondent, apparently in order that the court's preferred interpretation be adopted. *Id.* at 11a.

This mission was performed under the banner of *Chevron USA, Inc.* v. *NRDC*, 467 U.S. 837 (1984), pursuant to which the majority considered whether Respondent's

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[9] The United States did not seek further review of the Federal Circuit's decision in *Glaxo*. The district court's opinion in *Glaxo* is notable for its extended analysis and criticism of the district court's decision in this case. *See Glaxo Operations UK Ltd.* v. *Quigg*, 706 F. Supp. 1224, 1230-33 (E.D. Va. 1989).

construction of the assertedly ambiguous statute was reasonable. The court concluded it was not. Respondent urged that the word "including" in the phrase "active ingredient (*including* any ester or salt of the active ingredient)" was ambiguous—a position it never before had taken—and should be read to embrace all minor variations of the active ingredient, not merely the specific relationships of "salt" and "ester" set forth by Congress. The majority correctly rejected this construction as "linguistically infeasible." App., *infra*, 9a.

The majority then considered Petitioner's construction, one of the two meanings the statute was held capable of supporting. The majority acknowledged that Petitioner had offered "the more obvious linguistic construction of the statute," App., *infra*, 9a, and conceded that the legislative history offered no basis to dispute that construction. Nevertheless, the majority rejected the statute's plain meaning as "farfetched," speculating without citation that Congress "seems to have had [in mind]" a meaning different from that set forth in the statutory language. *Id.* at 7a, 10a. The majority did not discuss or even refer to the contrary reasoning of the Federal Circuit in *Glaxo*.

Although the majority stated its view of what the statute "seemed" to mean, it declined pursuant to *Chevron* to construe the supposedly ambiguous statute for Respondent, instead directing that the case be remanded to the agency for another try. With one of two permissible statutory constructions ruled out, however, Respondent's discretion to construe the statute would appear nonexistent. Adding to the confusion, the majority volunteered in *dicta* the baffling suggestion that FDA might fasten on yet an entirely different statutory term, "active ingredient," and construe it differently to mean "active moiety" in the market exclusivity provisions. App., *infra*, 6a-7a. This is precisely the construction Respondent had already forcefully rejected when it sought reconsideration before the District Court. *Id.* at 27a-28a.

The dissent in the court of appeals concluded, along with the district court below and both federal courts in *Glaxo*, that the ten-year exclusivity provision indeed was clear and unambiguous and must be honored by both Respondent and the courts. It observed that the majority, rather than truly believing the statute was ambiguous, seemed rather just to disagree with the wisdom of applying the statutory language as written to DEPAKOTE. App., *infra*, 14a. The dissent added that the majority's concerns over application of the plain meaning of the statutory language were entirely speculative and illogical, but more important represented an impermissible substitution of judicial (and administrative) judgment for that of Congress. *Ibid.* In conclusion, the dissent observed that the majority's theory of statutory construction—that any statutory ambiguity, "however remote, slight or fanciful," takes a case out of the hands of the courts and Congress and turns it over for administrative resolution—was inconsistent with *Chevron* and later decisions and upset the proper balance of powers under the Constitution. *Id.* at 23a-24a.

Abbott filed a Petition for Rehearing and Suggestion for Rehearing *en banc*. The court of appeals ordered *sua sponte* that Respondent submit a brief in response, and the motions ultimately were denied after two months' consideration. App., *infra*, 100a-101a.

REASONS FOR GRANTING THE PETITION

This case addresses a critical aspect of major legislation that fundamentally altered the process through which generic copies of pharmaceutical products are approved for sale. That legislation—the Hatch-Waxman Amendments—represented a compromise fashioned by Congress to reconcile important and competing national interests. The legislative compromise was reflected in the clear, precise, and unambiguous language of the market exclusivity provisions, and neither Respondent nor the

court of appeals had authority to alter it. But that is precisely what they did.

Respondent, displeased with the language chosen by Congress, chose to recast the market exclusivity provisions in terms of the language it wishes Congress had used, but did not. Respondent's failure to heed the command of Congress is reflected in its decision to deny ten-years' exclusivity to DEPAKOTE, and is codified for application to all new drug products in proposed regulations implementing the Hatch-Waxman Amendments. *See* 54 Fed. Reg. 28872, 28,896-98 (1989).

The court of appeals similarly deemed itself authorized to amend the language chosen by Congress, cloaking its impermissible legislative activities in a spurious claim of ambiguity in the statutory text—an ambiguity that theretofore had gone undetected by every court and every party to have considered the language at issue. No colorable ambiguity exists in the language, as the contrary decision of the Federal Circuit confirms, and the majority's attempt to improve upon an Act of Congress, no matter how sincerely motivated, cannot be allowed to stand. The court of appeals majority has denied to Petitioner rights secured by federal statute, and in the process effectively voided proposed regulations intended by Respondent to offer guidance to the pharmaceutical industry on the operation of the new legislation. The result is confusion: The holding of the court is flatly at odds with the position taken in Respondent's proposed regulations, and both are inconsistent with the statute's plain language and the holding of the Federal Circuit in *Glaxo*.

Review is also required because the decision of the court of appeals majority does violence to the high regard for statutory language that this Court's decisions have counseled time and time again in recent years. If the statute at issue in this case may be called ambiguous as a matter of law, so can any. And with such unprincipled statutory analysis comes a device by which any

court may usurp so much of the legislative function as it sees fit.

I. THE COURT OF APPEALS MAJORITY IMPROPERLY REWROTE THE STATUTORY CRITERIA FOR DETERMINING A DRUG'S PERIOD OF MARKET EXCLUSIVITY UNDER THE HATCH-WAXMAN AMENDMENTS

A. The Market Exclusivity Provisions Are Clear And Unambiguous, And Cannot Support The Spurious Claim of Ambiguity Advanced By The Court of Appeals Majority

It is axiomatic that the process of statutory construction begins with the text itself, and requires a court to give legislation a plain, not tortured reading. "We begin with the language employed by Congress and the assumption that the ordinary meaning of that language accurately expresses the legislative purpose." *FMC Corp.* v. *Holliday*, 111 S. Ct. 403, 407 (1990). *See also Pavelic & LeFlore* v. *Marvel Entertainment Group*, 110 S. Ct. 456, 460 (1990) (court should implement what text "most naturally seems to say"); *United States* v. *Ron Pair, Inc.*, 489 U.S. 235, 241 (1989) (statute unambiguous based upon its "natural reading"); *TVA* v. *Hill*, 437 U.S. 153, 173 (1978) (rejecting construction where Court "would be forced to ignore the ordinary meaning of plain language").

The "plain meaning" doctrine rejects the notion that any theoretical imprecision in statutory language, no matter how illogical or improbable, is sufficient to defeat what otherwise is the discernible intent of Congress. *See, e.g., United States* v. *James*, 478 U.S. 597, 604-05 (1986) (neither "ingenuity" nor mere "assertions of ambiguity" are sufficient to supplant the "ordinary meaning of the words used by Congress" (citations omitted)). As this Court observed in *Amoco Production Co.* v. *Gambell*, 480 U.S. 531, 548 (1987), "language seldom attains the

precision of a mathematical symbol;" yet despite this the judiciary must honor language whose meaning nonetheless is clear. *See also FMC Corp.* v. *Holliday*, 111 S. Ct. at 407 (although provisions "not a model of legislative drafting," "[t]heir operation is nevertheless discernible") (citation omitted); *Dole* v. *Steelworkers*, 110 S. Ct. 929, 937 (1990) ("While the grammar of this text can be faulted, its meaning is clear"). The plain meaning doctrine exists, in other words, as an essential protection against judicial and administrative lawmaking.

This extended discussion of fundamental principles of statutory construction is warranted because it is precisely these principles that the court of appeals majority chose to ignore. There can be no dispute that the language characterized by the majority as ambiguous in fact can support only the meaning ascribed to it by Petitioner and the Federal Circuit. DEPAKOTE is entitled to ten years' exclusivity because its "active ingredient (including any ester or salt of the active ingredient)" has not previously been approved by Respondent. As was the case in *Northbrook Nat. Ins. Co.* v. *Brewer*, 110 S. Ct. 297, 299 (1989), this language "could not be more clear."

The Federal Circuit observed that this statutory text has an "unambiguous" "plain meaning," and that each of the text's component terms had "well-defined, ordinary, common meanings" when enacted by Congress.[10] *Glaxo Operations UK Ltd.* v. *Quigg*, 894 F.2d 392, 395 (Fed. Cir. 1990). DEPAKOTE satisfies this unambiguous statutory test to qualify for ten-years' exclusivity: Neither its active ingredient, divalproex sodium, nor an ester or salt of divalproex sodium, had been approved by FDA prior to the approval of DEPAKOTE, as all parties agree.

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[10] The nearly-identical language of the patent term extension provisions of the Hatch-Waxman Amendments construed in *Glaxo* read "active ingredient of . . . a new drug . . . including any salt or ester of the active ingredient . . . ." *See* 35 U.S.C. § 156(f)(2).

The court of appeals majority, however, purported to find ambiguity in this clear language—and with it, the key to open the door to rewriting the statute in accordance with its own policy preferences. The majority's confusing discussion focuses not on the ten-year exclusivity provision applicable to DEPAKOTE but on its two-year counterpart, which applies if a "drug, *an* active ingredient (including any ester or salt of *the* active ingredient) of which" had previously been approved (emphasis added by court of appeals). The majority maintains that the word "the," contrasted with the word "an," makes unclear whether the "active ingredient" referred to in the parenthetical is that of the drug in question, or is that of *any* drug ever approved. App., *infra*, 7a-8a. This simply cannot be so.

"The language and punctuation Congress used cannot be read in any other way" than that advanced by the Federal Circuit and Petitioner. *See United States* v. *Ron Pair, Inc.*, 489 U.S. at 242. There is only one "active ingredient" referred to in the statute—that of the drug whose exclusivity is at issue (here, DEPAKOTE). It is to this "active ingredient" that the parenthetical obviously and indisputably refers. Similar attempts by courts to infuse ambiguity into clear statutory language by ignoring simple grammatical rules have been routinely rejected by this Court. *See Pavelic & LeFlore* v. *Marvel Entertainment Group*, 110 S. Ct. at 458-59; *Chan* v. *KAL Ltd.*, 490 U.S. 122, 129 n.3 (1989). The fact that the phrase begins by asking whether the drug contains "an" active ingredient simply recognizes that a drug product may contain more than one, and that only one previously-approved active ingredient is enough to defeat ten-years' exclusivity. Indeed, for grammatical reasons the redoubtable "an" does not even appear in the ten-year exclusivity provision applicable to DEPAKOTE or in the formulation of the phrase in the patent term

extension provision addressed in *Glaxo*. Its presence in the two-year provision should not be permitted to disrupt what the coherent structure of the Hatch-Waxman Amendments obviously requires. *Cf. Dole* v. *Steelworkers*, 110 S. Ct. 929 (1990); *Pennsylvania* v. *Union Gas Co.*, 491 U.S. 1, 10 (1989).

B. No Ground Exists on Which To Refuse To Implement The Statute's Plain Meaning

Congress has spoken clearly and unambiguously on a specific question—the criteria for determining which exclusivity period should apply to any drug—and both Respondent and the court of appeals were required to respect Congress' decision. *Chevron USA, Inc.* v. *NRDC*, 467 U.S. 837 (1984). This Court frequently in recent years has had occasion to repeat its paramount deference to statutory language, and to delineate the narrow exceptions to the rule that when the statutory language is clear, "the judicial inquiry is complete." *See Rubin* v. *United States*, 449 U.S. 424, 430 (1981). A party seeking to overturn "plain and precise" statutory language "faces a daunting challenge"—it must show "clear evidence that reading the language literally would thwart the obvious purpose of the Act." *Mansell* v. *Mansell*, 490 U.S. 581, 592 (1989).

Here, by contrast, no evidence *of any kind* exists to compromise the clear meaning of the statutory language. The court of appeals majority concedes as much, acknowledging that the legislative history sheds no light on the precise meaning of the market exclusivity provisons.[11] App., *infra*, 8a. Indeed the majority casts aside the statute's plain meaning on what, in the acknowledged absence of legislative history, must be the naked speculation that the statute's words do not reflect what "Con-

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[11] The present form of the market exclusivity scheme was added *in toto* as an amendment on the House floor, 130 Cong. Rec. 24,421-24,439 (1984), and generated no specific discussion on the question presented in this case.

gress [seems to have] had in mind." *Id.* at 7a. The majority's only attempt to support its apparently telepathic insight is its assertion that under one set of facts the plain language would produce a "farfetched" result assertedly "not consistent with any legislative goal." *Id.* at 10a. The concern is misplaced.[12] More to the point, it is a patently inadequate ground upon which to overturn clear statutory language.

It is settled that courts are required to implement an unambiguous congressional command even where it would produce seemingly anomalous or undesirable results. *See, e.g., Hallstrom* v. *Tillamook County*, 110 S. Ct. 304, 311 (1989) (recognizing damage to environment that might result from plain language construction of statute, but concluding that "problem arises as a result of the balance struck by Congress"); *Northbrook National Ins. Co.* v. *Brewer*, 110 S. Ct. at 300 (implementing "precise wording" of statute even though "somewhat anomalous" results and "seeming incongruity" would occur). *See also Pavelic & LeFlore* v. *Marvel Entertainment Group*, 110 S. Ct. at 459-460; *Board of Educ. of the Westside Community Schools* v. *Mergens*, 110 S. Ct. 2356, 2367 (1990); *Board of Governors of Federal Reserve System* v. *Dimension Financial Corp.*, 474 U.S. 361, 374 n.7 (1986). What is required to overcome a clear statutory command is a "clearly expressed legislative intention to the contrary," *Hallstrom* v. *Tillamook County*, 110 S. Ct. at 310, quoting *Consumer Product Safety Commission* v. *GTE Sylvania, Inc.*, 447 U.S. 102, 108 (1980), not a

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[12] The majority's concern was as follows: "[I]f an original drug application has an active ingredient in the form of a salt, a drug company cannot obtain extended protection by merely filing a new application for a drug with an active ingredient in a non-salt form, but if it does the reverse, as in this case, it can." App., *infra*, 10a. This result, as a factual matter, is completely rational, as Abbott observed in the court of appeals and that at least one court has expressly so found. *See Glaxo Operations UK Ltd.* v. *Quigg*, 706 F. Supp. 1224, 1229-30 n.12 (E.D. Va. 1989), *aff'd*, 894 F.2d 392 (Fed. Cir. 1990).

vague notion in the absence of legislative history that the plain language in one hypothetical case might produce what the court perceives is a "farfetched" result.

The majority's failure to defer to the statutory language is made even more alarming by the nature of the legislation in question. The Hatch-Waxman Amendments generally, and the market exclusivity provisions in particular, reflect a legislative mediation between important interests and constituencies. "There is no magic to the distinctions made by the various [market exclusivity] periods; rather, they reflect the legislative compromises implicit throughout the Act." J. Wheaton, *Generic Competition And Pharmaceutical Innovation: The Drug Price Competition And Patent Term Restoration Act of 1984*, 35 Cath. U. L. Rev. 433, 463 (1986). This Court has recognized that legislation can serve several purposes, and has warned that statutory language reflecting congressional compromises should not be tinkered with under the guise of implementing what a court perceives to be a statute's general aims. *See, e.g., Board of Governors of Federal Reserce System* v. *Dimension Financial Corp.*, 474 U.S. 361, 373-74 (1986); *American Tobacco Co.* v. *Patterson*, 456 U.S. 63, 68-69 (1982). In the absence of evidence of contrary legislative intent, a court may not "assume that Congress intended anything more than it had stated in unambiguous terms. . . . We cannot doubt that Congress meant what it said." *Northbrook National Inc. Co.* v. *Brewer*, 110 S. Ct. at 301.

II. THE MAJORITY FAILED TO ACCORD THE MARKET EXCLUSIVITY PROVISIONS THE PRESUMPTION OF VALIDITY TO WHICH THEY ARE ENTITLED

The majority's improper reliance on the absence of legislative history supporting the plain-language interpretation of the market exclusivity provisions raises a separate concern that warrants review by this Court. The majority effectively placed upon Congress, and sepa-

rately, upon Petitioners, an obligation to justify every conceivable implication of the congressional scheme, or face the invalidation of that scheme by any court inclined to second-guess how Congress has chosen to address a particular problem. App., *infra*, 8a. The court of appeals has it backwards. Legislation generally is entitled to a presumption of rationality, even greater than that accorded administrative actions. *Motor Vehicle Mfrs. Ass'n* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 n.9 (1983). There is no requirement of proof that the application of a statute to every hypothetical case have been considered by Congress and acknowledged as the intended result of legislation. It is not the law that a statute's effect is limited to those situations expressly referred to in the legislative history. *Pittston Coal Group* v. *Sebben*, 488 U.S. 105, 115 (1988).

Mansell v. *Mansell*, 490 U.S. 581 (1989), for example, involved the construction of a statute that, on its face, prohibited a divorcing spouse from obtaining community property rights to a certain portion of a veteran's military pension. The plain-language construction was seen as capable of "inflict[ing] economic harm on many former spouses," and the spouse argued that Congress could not have intended that result. *See id.* at 594. Indeed, no affirmative rationale for the rule appeared in the legislative history. This Court held specifically that none was needed:

> The legislative history does not indicate the reason for Congress' decision to shelter from community property law that portion of military retirement pay waived to receive veterans' disability payments. But the absence of legislative history on this decision is immaterial in light of the plain and precise language of the statute; Congress is not required to build a record in the legislative history to defend its policy choices.

Id. at 592 (footnote omitted). *See also United States* v. *Ron Pair, Inc.*, 489 U.S. at 240-41.

In this case, however, the court of appeals required exactly that. Compounding its own speculation as to what Congress "seems" to have intended, the majority surmises that legislators did not "have in mind" the case presented here because there is no record of such consideration in the legislative history. App., *infra*, 7a-8a. The majority on this ground alone concluded that Congress "did not directly address the 'precise question at issue'" (*citing Chevron*, 467 U.S. at 843), and transferred responsibility for giving meaning to the provisions from Congress to itself and the administrative agency. *Id.* at 11a. This is in direct conflict with *Pittston Coal Group* v. *Sebben* and *Mansell* v. *Mansell*, and undermines the court's proper constitutional role. It is particularly disingenuous given Congress' stated intent that market exclusivity provisions encourage research and development by pharmaceutical manufacturers, who presumably are expected to plan their activities based upon the financial incentives communicated by the statute's plain language. The absence of affirmative discussion in the legislative history in no way compromises the validity of the enactment, and in no way reduces the obligation of the court to implement clear and unambiguous statutory language.

CONCLUSION

The Petition for Certiorari should be granted.

Respectfully submitted,

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APPENDICES

APPENDICES

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued September 7, 1990 Decided December 7, 1990

No. 88-5260

ABBOTT LABORATORIES,
Appellant

v.

FRANK D. YOUNG, DR., COMMISSIONER,
FOOD AND DRUG ADMINISTRATION

No. 89-5183

ABBOTT LABORATORIES,
Appellant

v.

FRANK D. YOUNG, DR., COMMISSIONER,
FOOD AND DRUG ADMINISTRATION

Appeals from the United States District Court
for the District of Columbia
(Civil Action No. 88-00474)

Harold D. Murry, Jr., with whom *Robert P. Reznick* was on the brief, for appellant. *Bryan Jay Yolles* also entered an appearance for appellant.

Irene M. Solet, Attorney, Department of Justice, with whom *Stuart M. Gerson*, Assistant Attorney General, *Jay B. Stephens*, United States Attorney, and *Anthony J. Steinmeyer*, Attorney, Department of Justice, were on the brief, for appellee. *Jacqueline H. Eagle*, Attorney, Department of Justice, also entered an appearance for appellee.

Peter R. Mathers for *amicus curiae* Par Pharmaceutical, Inc., urging affirmance.

Before: MIKVA, EDWARDS, and SILBERMAN, *Circuit Judges.*

Opinion for the Court filed by *Circuit Judge* SILBERMAN.

Dissenting Opinion filed by *Circuit Judge* EDWARDS.

SILBERMAN, *Circuit Judge*: This is an unusual case in which both the appellant and the government present us with unreasonable interpretations of a statute we think ambiguous. We therefore direct the district court to remand to the agency for reconsideration.

I.

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (the "Hatch-Waxman Amendments"), amending the Federal Food, Drug, and Cosmetics Act, 21 U.S.C. §§ 301-392. The statute created a new system for protecting both the interests of drug manufacturers who produce new drugs and the interests of generic drug manufacturers and their consumers. Facing the classic question of the appropriate trade-off between greater incentives for the invention of new products and greater affordability of those products, Congress struck a balance between expediting generic drug applications and protecting the interests of the original drug manufacturers. *See* H.R. REP. NO. 98-857 (Pt. 1), 98th Cong., 2d Sess. 14, 15, *reprinted in* 1984 U.S. CODE CONG. & ADMIN. NEWS 2647, 2648. It reserved a longer period of market exclusivity

for newly developed drugs than for drugs for which the approval process had already been completed in a prior application. The statute gives the original drug producer a specified period of market exclusivity depending primarily on the pharmaceutical novelty of a drug.

This case requires us to determine the scope of the exclusivity provisions, in particular the meaning of the phrase "active ingredient (including any ester or salt of the active ingredient)." 21 U.S.C. § 355(j)(4)(D)(i) and (v). The full statutory language is set out in the margin, but the key parts of the two relevant subsections of the statute state that a two year exclusivity period attaches to a drug whose new drug application ("NDA") "includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another [NDA]," 21 U.S.C. § 355(j)(4)(D)(v) and a ten year exclusivity period attaches to a drug whose NDA has "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other [NDA]," 21 U.S.C. § 355(j)(4)(D)(i).[1] Congress

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[1] If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of *the* active ingredient) *of which* has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b) of this section.

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, *which* includes an active ingredient (including any ester or salt of the active ingredient) *that* has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval

thereby sought to encourage innovation in the drug industry, by rewarding a pioneer drug with a ten year exclusivity, while protecting consumers from unduly high prices by refusing to give a long period of market exclusivity to drugs which required no new research effort.

In 1978 the Food and Drug Administration ("FDA") approved for marketing Abbott Laboratories' ("Abbott") new drug application for Depakene, an anticonvulsant drug prescribed for control of epileptic and other seizures. The chemical ingredient of Depakene that performs the drug's therapeutic function is valproic acid. Valproic acid is both an "active ingredient" (the substance prior to introduction into the human body) and an "active moiety" (the substance that creates the actual therapeutic effect within the body). In 1982, the FDA approved Abbott's new drug application ("NDA") for another drug, Depakote, also prescribed for control of seizures. In its Depakote NDA, Abbott relied exclusively on the safety and efficacy findings established in the course of the prior Depakene application, because the "active moiety" of Depakote was the very same valproic acid. Depakote's active ingredient, we are told, is divalproex sodium which is converted into the valproic acid within the human body.

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of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from September 24, 1984.

21 U.S.C. § 355(j)(4)(D)(i) and (v) (emphases added).

Both (D)(i) and (D)(v) apply to the transition period under the statute, from January 1, 1982 to September 24, 1984, during which the ten year and two year exclusivity periods apply. Sections (D)(ii), (iii), and (iv) control the applicable exclusivity periods after September 24, 1984. Because the instant case arose during the transition period, only (D)(i) and (D)(v) are at issue here. We note that the same language is used for determining the applicable periods of exclusivity for drugs introduced after September 24, 1984—the only difference in the statutory scheme is the length of the exclusivity periods.

Apparently divalproex sodium presents fewer gastrointestinal side effects than the valproic acid. Although the issue was disputed, the agency found divalproex sodium to be a salt of valproic acid.[2] In simple terms, a salt is a chemical compound created when the "parent" substance reacts with another chemical. A salt is "formed when the hydrogen of an acid is replaced by a metal or its equivalent." *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392, 393 n.3 (Fed. Cir. 1990), *citing The Condensed Chemical Dictionary* 907 (G. Hawley rev. 10th ed. 1981). FDA determined that Depakote could only be granted a two year period of market exclusivity pursuant to the statute because it was a salt of the active ingredient of the prior-approved Depakene. On August 29, 1986 Abbott Submitted a Citizen Petition to the FDA pursuant to 21 C.F.R. § 10.30 requesting a ten year exclusivity. The FDA denied Abbott's petition, *Abbott Labs*, Docket No. 86P-0367 (FDA February 11, 1988), and Abbott filed a suit in the district court. It appeals from a judgment below which affirmed the agency decision. *Abbott Labs. v. Young*, 691 F. Supp. 462 (D.D.C. 1988).

II.

Pursuant to the Supreme Court's guidance in *Chevron*, we must first determine whether Congress manifested an "unambiguously expressed intent" that resolves this dispute over the statute's meaning. *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984). Of course, the language of the statute itself is always the best indication of congressional intent. Abbott argues, with the support of the Federal Circuit, that the "plain meaning" of the language supports its interpretation. Both Abbott and the Federal Circuit, *see Glaxo*, 894 F.2d at 393-94, focus only on the phrase

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[2] The FDA based its decision about the chemical relationship between Depakote and Depakene in part on an affidavit submitted by Dr. Robert H. Wood, of which Abbott was not given notice.

"active ingredient," claiming it has a well understood meaning. The district court, on the other hand, thought that the usage of the reference words "which," "of which," and "that" in sections (i) and (v) created an overlap and therefore an irreconcilable conflict between the sections because the same active ingredient was ostensibly covered by both provisions, resulting in different periods of exclusivity mandated for the same substance. *See* 691 F. Supp. at 472. The government disavows the district judge's perceived irreconcilable conflict.[3] Instead, the government reads the parenthetical phrase ("including any ester or salt of the active ingredient") to permit an interpretation of "active ingredient" that includes even more than salt or ester derivatives. According to the government, that phrase can be interpreted to mean that Congress was using the term active ingredient loosely, possibly as a virtual synonym for active moiety.

Indeed, it was at least suggested in an agency letter, subsequent to the decision in Abbott's case, that the phrase "active ingredient" itself, even without the parenthetical, could be interpreted to include active moiety notwithstanding that the FDA construes that term narrowly in another section of the act, 335(j)(4)(D). *See McNeil Pharmaceutical* 6, Docket No. 87P-0339 (FDA July 26, 1989). The agency appears to contend that the different purpose of that other section 335(j)(4)(D) (providing for expedited approval of generic drugs so agency caution is indicated) justifies a different interpretation of the same phrase. We note that it is not impermissible under *Chevron* for an agency to interpret an imprecise term differently in two separate sections of a statute which have different purposes. *See National Ass'n of Casualty and Surety Agents v. Board of Governors of the Fed. Reserve Sys.*, 856 F.2d 282, 287 (D.C. Cir. 1988) (up-

[3] Of course the district judge's construction of the statute is not entitled to deference as is the agency's—if the agency's interpretation meets the *Chevron* standard.

holding different agency interpretations of same phrase when based on reasonable explanation), *cert. denied*, 109 S. Ct. 2430 (1989); *Comite Pro Rescate v. Sewer Auth.*, 888 F.2d 180, 187 (1st Cir. 1989) (same), *cert. denied*, 110 S. Ct. 1476 (1990). But we cannot consider whether active ingredient is such a term because the agency did not in its decision on Abbott's application employ this theory.

Putting aside for a moment the relative merits of the various constructions offered, we first conclude the language is ambiguous as it relates to the issue before us. The parenthetical phrase ("including any ester or salt of *the* active ingredient") can refer to *either* the active ingredient of the original approved drug *or* to the active ingredient in the new drug, depending on how "the" in the parenthetical and the words surrounding the parenthetical—"no active ingredient . . . of which has been approved"—is interpreted. In other words, the definition of an active ingredient as including both the active ingredient and an ester or salt of *the* active ingredient can refer *both* to the active ingredient in the earlier and the later drug application, which would be the proper reading if Congress had in mind, as it seems to have had, that an active ingredient was to be regarded for purpose of this portion of the statute as equivalent to an ester or salt of itself.

In this section of the Act, Congress was concerned with defining the chemical entity on which a subsection (j) (generic drug) application is based.[4] When Congress used the definition "*an* active ingredient (or the salt or ester

[4] Subsection (b) applications are new drug applications for original drugs, while subsection (j) applications are generic drug applications which face reduced barriers to FDA approval. The length of market exclusivity simply determines *when* a subsection (j) application is allowed, which is determined by reference by the new drug application for original drugs, *i.e.*, subsection (b) applications.

of *the* active ingredient)," § 355(j)(4)(D)(v) (emphasis added), that definition arguably referred to *all* the subsection (b) applications in question. The FDA's authorization to approve a generic drug (subsection (j) application) depends on its relationship to all original drugs (subsection (b) applications). Therefore, Congress may have intended for its definition—"*an* active ingredient (including any salt or ester of *the* active ingredient)," § 355(j)(4)(D)(v)—to refer to the universe of all subsection (b) applications. Thus, the ambiguity of reference in the phrase reflects the possibility that it can refer to the latest subsection (b) application as well as all prior subsection (b) applications. Although our dissenting colleague asserts the language has a plain meaning, he does not explain why we are incorrect in perceiving this ambiguity.[5]

III.

Since we have discovered nothing in the legislative history that could be thought to embody the express intent that the language does not yield, we pass on to the second step of *Chevron* and ask whether the government's construction falls within the bounds of reasonableness. We think it does not—at least its primary argument presented before us does not. The "reasonableness" of an agency's construction depends on the construction "fit" with the statutory language as well as its conformity to statutory purposes. We cannot agree with the government's unconvincing attempts to employ the "including"

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[5] We note that the Act includes other ambiguities hinging on unclear references. *See Eli Lilly & Co. v. Medtronic, Inc.*, 110 S. Ct. 2683 (1990) (structurally unclear whether "a Federal law which regulates the manufacture, use, or sale of drugs" applies to individual provisions regulating drugs or to the entirety of any Act which has parts regulating drugs). In that case the Court had to pick its way between a more natural reading that yielded an implausible meaning, and an interpretation that gave the unclear phrase "a meaning it simply will not bear." *Id.* at 2687.

clause to cover all possible permutations of active ingredient. This case differs from instances where an "including" clause is designed to merely illustrate a few examples of the general category, *see, e.g., Puerto Rico Maritime Shipping Auth. v. ICC*, 645 F.2d 1102, 1112 n.26 (D.C. Cir. 1981). It is simply not plausible to read "including any salt or ester" as merely illustrative, to mean including *any* form that eventually produces the same active moiety. In other words, we reject the government's interpretation as *linguistically* infeasible even though logically possible.

Once we reject the agency's interpretation of the statute as unreasonable it does not follow that appellant's competing construction must be adopted. Even if we thought appellant's interpretation were reasonable we could not accept it if we perceived still other possible reasonable constructions. It is, after all, for the agency to make the choice between such alternatives. But in this case we do not believe Abbott's suggested interpretation *is* reasonable.

Abbott argues that even if divalproex sodium is a salt of valproic acid,[6] the statute precludes the FDA from treating the two chemicals as the same active ingredient because of the sequence of applications. To be sure, Abbott's interpretation, at first reading, is the more obvious linguistic construction of the statute—that active ingredient refers in this case to divalproex sodium. The parenthetical phrase ("including any ester or salt of the

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[6] The FDA found that the divalproex sodium is a salt of valproic acid but Abbott continues to deny it. This is partly a substantive chemical question and partly a procedural issue—whether the agency improperly relied on an affidavit not brought to the attention of Abbott. Since we are remanding in any event to give the agency an opportunity to parse the language of the statute again, the agency might choose to adopt a procedure that would obviate any need for us to consider the affidavit issue if it remains relevant to the agency's decision.

active ingredient"), according to Abbott, refers only to the original drug, the active ingredient "of which has been approved."

Abbott's interpretation then, unlike the FDA's, is possible linguistically but fails to serve any conceivable statutory purpose. It would mean that if an original drug application has an active ingredient in the form of a salt, a drug company cannot obtain extended protection by merely filing a new application for a drug with an active ingredient in its non-salt form, but if it does the reverse, as in this case, it can. That construction appears to be farfetched because it is not consistent with any legislative goal: Abbott can advance no hypothetical reason why Congress (or indeed any of the interest groups) would have wanted the degree of protection a drug received to turn on this variable sequence.[7] Abbott's reading promotes neither the interests of the research-oriented pharmaceutical industry nor the generic drug industry in a rational way, producing instead a windfall depending on an accident of chemical nomenclature. We have not been offered *any* scientific, technical, economic or other explanation why Congress would intend the grant of a ten year market exclusivity to depend on the temporal sequence in which subsection (b) applications were approved and the counsel could not suggest any when pressed on this point. It appears, then, entirely serendipitous that in this case Abbott sought an application for the salt of valproic acid after *first* applying for valproic acid. Thus, under Abbott's interpretation, if a pharmaceutical manufacturer developed two usable drugs, one a salt of the other, he could gain extra protection by

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[7] Abbott's brief did refer to a district judge's speculation that deriving ester or salt from an acid requires a greater effort than the reverse process, *see Glaxo Operations UK Ltd. v. Quigg*, 706 F. Supp. 1224, 1229-30 n.12 (E.D. Va. 1989), *aff'd*, 894 F.2d 392 (Fed. Cir. 1990), but the district court offered no support for that notion and at oral argument Abbott's counsel, when asked, did not put forth that hypothesis.

applying for approval of the acid first, followed by the salt, but not under the reverse sequence.

If Congress truly intended the sequential distinction that Abbott urges, it would have drafted (it would have *had* to draft) quite different language in a different structure such as

> If an application submitted under subsection (b) of this section is for a drug which contains an active ingredient that is also contained in a previously approved drug, then . . . . For purposes of this section an active ingredient in the previously approved drug includes an ester or salt of an active ingredient in the previously approved drug, but in the event that an ester or salt of the original active ingredient is filed as an active ingredient of the subsequent NDA, there is no disqualification.

That Abbott's interpretation passes first reading suggests to us that Congress did not focus on the reverse sequence of application; not that it intended to address a sequential distinction. Ambiguity of language typically appears when the draftsman does not have in mind the manner in which the norm set forth in the statute will apply to a particular situation. We think that occurred here; Congress did not directly address the "precise question at issue," *Chevron*, 467 U.S. at 843, and therefore the FDA (not the judiciary) is entitled to place its reasonable construction on the ambiguous statute.

* * * *

Accordingly, we remand this case to the district court with instructions, in turn, to remand to the agency. We hold only that the statute is ambiguous; the reliance the government places on the including clause is an unreasonable construction and that Abbott's interpretation of the statute is also unreasonable. Beyond that, we may not proceed since we have no authority to place a construction on the statute that the agency has not offered.

EDWARDS, *Circuit Judge*, dissenting:

PROLOGUE

This is a bizarre case: Every reasonable consideration furnishing a basis for judgment favors the appellant; yet, the majority cannot bring itself to reach the result that is compelled by the record before it.

We reject the decision of the District Court, for it fails to comport with the terms of the statute. . . . We also recognize that the FDA—the agency to which we owe deference if this case is analyzed under "step two" of *Chevron U.S.A., Inc. v. NRDC*, 467 U.S. 837 (1984)—does not subscribe to the rationale underlying the District Court's decision. . . . We also reject the FDA's interpretation, because it, too, is at odds with the language of the statute and does not otherwise reflect a permissible reading of the disputed legislation. . . . We agree with the District Court that Abbott's interpretation *is* supported by the plain language of the statute, although the majority finds this result unpalatable. . . . And, finally, our decision today is in direct conflict with a judgment of a sister circuit. *See Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392, 395 (Fed. Cir. 1990).

Despite all of the foregoing, the majority has decided to remand this case to the agency to give it another shot at the issue. This makes no sense to me.

In 1978, the Food and Drug Administration ("FDA") approved a new anticonvulsant drug, called "Depakene," that had been developed by the appellant, Abbott Laboratories ("Abbott"). Depakene was effective in controlling seizures but caused harmful gastrointestinal side-effects in some patients. To avoid these side-effects, Abbott subsequently developed a new drug, called "Depakote," which was also effective in controlling seizures but which used a different "active ingredient" that was less prone

to irritating patients' digestive tracts. Thus, although the two drugs bear chemical similarities, Depakote represents a significant improvement over the earlier drug.

Abbott filed a new drug application for approval to market Depakote in December of 1981. The FDA approved the new drug on March 10, 1983. Thereafter, on September 24, 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (the "Act" or "the Hatch-Waxman Amendments"), which was intended to allow a manufacturer to obtain approval to market a drug without performing clinical tests normally required to support a full new drug application and, also, to provide market exclusivity for innovative drugs approved by the FDA. Under Title I of the Act, there are five categories of drugs eligible for varying periods of market exclusivity ranging from two years to 10 years. Relying on 21 U.S.C. § 355(j)(4)(D)(i) (hereinafter "subsection (i)"), which applies to drugs approved by the FDA between January 1, 1982, and September 24, 1984, Abbott sought 10 years of market exclusivity for Depakote.

Subsection (i) applies to "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application"; and Abbott claimed that the prior approval of Depakene did not bar 10-year exclusivity for Depakote, because the "active ingredient" for the two drugs is different and because the latter drug's active ingredient (including any ester or salt of it) had never before been approved by the FDA. The FDA rejected this claim, applying instead the two-year market exclusivity protection of 21 U.S.C. § 355(j)(4)(D)(v) (hereinafter "subsection (v)"), because Depakene and Depakote "shared the same active moiety." Brief for Appellee at 9. In other words, the FDA ignored the literal terms of the statute (focusing on "active moiety" in place of "active ingredient"), because, in the agency's view, Congress intended "to provide the maxi-

mum period of market protection only to the most innovative drugs which require the largest expenditure of resources to develop." *Id.* at 14. The agency concedes that "active ingredient" and "active moiety" are not the same; and the agency can point to no statutory provision supporting the gloss that it has placed on subsection (i).

The majority, while shunning the FDA's statutory construction, agrees with the conclusion that Depakote should obtain only the shorter, two-year period of market protection. In reaching this judgment, the majority, like the FDA, ignores the plain meaning of the statute because it believes that, if enforced as written, the statute would produce arbitrary results. I dissent because I believe the majority's conclusion is based on largely groundless conjecture, and because it is our task as judges to apply the statute as it is written, not as we think it ought to have been written.

I.

As the majority correctly notes, the Hatch-Waxman Amendments were the product of compromise. The Act emerged from Congress' efforts to balance two conflicting policy objectives: to induce name-brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market. *See Mead Johnson Pharmaceutical Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988); H.R. REP. No. 857, 98th Cong., 2d Sess., pt. 1, at 14-15, *reprinted in* 1984 U.S. CODE CONG. & ADMIN. NEWS 2647, 2647-48. The statutory provisions directly at issue here reflect one of the incentives Congress held out to name-brand pharmaceutical concerns in the trade-off, namely, market exclusivity for the pioneer drugs they bring to market. During the period of market exclusivity, the FDA will withhold approval of any generic copy.

In assessing the applicability of subsection (i) (the 10-year provision) versus subsection (v) (the two-year provision),[1] the critical question is whether the new drug for which market exclusivity is sought contains an "active ingredient (including any ester or salt of the active ingredient)" that has been previously approved by the FDA. *See* 21 U.S.C. §§ 355(j)(4)(D)(i) & (v) (1988). If the new drug's "active ingredient (including any ester or salt of the active ingredient)" *has* been previously approved by the FDA, then the new drug is entitled only to two years' protection under subsection (v); if it *has not*, then the drug may claim the full 10-year period of market exclusivity under subsection (i), the rationale being that the drug likely represents a more significant innovation.

All parties agree that Depakote, the drug for which Abbott seeks market exclusivity, bears many similarities to Abbott's previously approved Depakene. Both drugs are prescribed to control seizures and both do so by way of a common "active moiety," *i.e.*, the pharmacologically significant agent that actually accomplishes the intended therapeutic effect in the human body. The "active moiety" for both Depakote and Depakene is a substance known as valproic acid. The chief innovative development in Depakote is a modification of Depakene's initial dosage form, *i.e.*, its "active ingredient," that avoids undesirable side-effects associated with Depakene. Depakene uses valproic acid as its "active ingredient"—in effect introducing the "active moiety" directly into the body. This ap-

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[1] Subsection (i) and subsection (v), at issue here, apply only to new drugs approved by the FDA during a transitional "window" from January 1, 1982, through September 24, 1984. Drugs approved after September 24, 1984, are entitled to generally shorter periods of market exclusivity under subsections (ii), (iii) and (iv) of 21 U.S.C. § 355(j)(4)(D) (1988). Abbott's Depakote, the drug whose claim to market exclusivity is contested in this action, was approved on March 10, 1983, and its right to market protection is therefore governed by either subsection (i) or subsection (v) of the Act.

proach was effective in controlling seizures but resulted in gastrointestinal side-effects, leading Abbott to develop Depakote. Depakote uses a different substance, known as divalproex sodium, as its active ingredient. Divalproex sodium avoids the side-effects associated with the direct ingestion of valproic acid. Once divalproex sodium is ingested, however, the body converts it into valproic acid, which then accomplishes the intended effect of controlling seizures.

Although valproic acid was previously approved in Abbott's earlier application for Depakene, it is conceded by all parties that neither divalproex sodium nor any salt or ester of divalproex sodium had ever been previously approved by the FDA.

Abbott sought the maximum, 10-year period of market exclusivity under the statute based on the fact that neither the active ingredient of its new drug (divalproex sodium) nor any salt or ester of that active ingredient had ever before won FDA approval. The FDA concluded, however, that Depakote was entitled only to two years' market exclusivity. It justified this conclusion by a rather far-fetched reading of the statute: by using the word "including" in the statute, the agency argued, Congress meant to introduce an illustrative list of the sorts of chemical derivations of an active ingredient that, if previously approved, would deprive a new drug of the maximum, 10-year protection. The FDA was thus entitled, the argument goes, to insert the term "active moiety" into the statutory scheme in order to effectuate the alleged broader intentions of Congress to distinguish between drugs that represented entirely new chemical entities and those that were derivations of previously approved entities. By this reading, Depakote would be entitled to only two years' protection because its active moiety (valproic acid) had been previously approved in Depakene.

II.

I agree with the majority that the FDA's reading of the statute, which turns entirely on a purported ambiguity or implied delegation in the word "including," is implausible and must be rejected. I also agree with the majority that the reading offered by the District Court, which concluded that there is an irreconcilable conflict beween the two obviously complementary statutory provisions, must also be rejected. I disagree, however, with the majority's discovery of a new purported ambiguity in the statute, a discovery it uses to justify a remand to the FDA (along with a strong hint about how the agency should construe subsections (i) and (v)). Rather, I believe this case is properly resolved at the first step of the familiar *Chevron* doctrine, under which the court must adhere to the clear intention of Congress expressed on the face of the statute. *See Chevron U.S.A., Inc. v. NRDC*, 467 U.S. 837, 842-43 (1984).

The parties are in agreement that the terms used by the statute—active ingredient, salt and ester—have plain and established meanings in scientific and regulatory parlance. *See Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392, 395 (Fed. Cir. 1990). The only ambiguity asserted by the FDA pertains to the statute's use of the word "including," a claim this court properly dismisses. Thus, by the plain terms of the statute, Abbott's Depakote is entitled to 10 years of market exclusivity because the FDA had never previously approved Depakote's active ingredient (divalproex sodium) or any salt or ester of that ingredient.

The majority rejects the literal terms of the Act, not because the statutory language is actually ambiguous, but rather because it fears that applying the statute as written might produce arbitrary results. Although the majority acknowledges that Abbott's interpretation of the statute is the more obvious one, it rejects this view as

whimsical because of the supposed ability of a drug manufacturer to manipulate the length of market exclusivity it obtains under the statute by altering the sequence in which it markets certain drugs. For example, it is conceded that if Abbott had invented and won FDA approval for Depakote *before* it invented Depakene, the latter drug would be entitled only to two years' protection. This is because divalproex sodium, arguably a salt of Depakene's active ingredient, valproic acid, would then have been previously approved by the FDA, pushing the second drug into the compass of subsection (v). By reversing the order in which Governmental approval is sought, however, the manufacturer could obtain 10 years' protection for both drugs under Abbott's "plain language" reading of the statute. Such a result could not have been within Congress' intention, the majority concludes, and the statute's plain meaning must therefore be ignored.

There are at least two answers to the majority's argument. First, we have no basis for knowing whether it would be scientifically plausible to reverse the order of pharmaceutical invention in a case of this sort, or economically feasible to reverse the order in which Government approval is sought. Intuition suggests that a "derivative" drug is likely to be invented *after* the "parent" drug, rather than the other way around. Indeed, it would seem capricious, even absurd, for a pharmaceutical company to develop and attempt to market a drug (like Depakene) with harmful side-effects *subsequent to* the development of a better drug (like Depakote) that avoided those side-effects. And in this case there is clearly no danger that Abbott orchestrated its new drug applications to exploit the statute given that the statutory provisions at issue here apply ony retrospectively to conduct that occurred before the statute was enacted.

Furthermore, and more to the point, the parties offered no evidence either to support or refute the majority's hypothesis. There is simply no basis in the

record for the majority's blithe assumption that it is entirely serendipitous that Abbott invented Depakene before Depakote. I am loath to ignore the plain words of Congress based upon a counterintuitive supposition that is apparently groundless.

Second, even if the sequence of invention and approval could be manipulated to the manufacturer's advantage, there is nothing so outrageous about such a result to justify the majority's refusal to enforce the statute as Congress wrote it. While it is true that "a court should go beyond the literal language of a statute if reliance on that language would defeat the plain purpose of the statute," *Bob Jones Univ. v. United States*, 461 U.S. 574, 586 (1983), the Supreme Court ordinarily applies this canon only where it is clear that adherence to a statute's literal terms would produce a result flagrantly at odds with legislative purpose.[2] The result that would

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[2] In *Bob Jones*, for example, the Court upheld an IRS interpretive ruling that restricted tax-exempt status only to "charitable" institutions even though the relevant statute contained no such literal restriction. The Court held that it was proper for the IRS to depart from the "plain language" of the statute where strict application of that language would provide governmental aid to an organization that was itself at odds with "a most fundamental national public policy" of racial equality. 461 U.S. at 593. The Court in that case found "unmistakable evidence that, underlying all relevant parts of the Code, is the intent that entitlement to tax exemption depends on meeting certain common-law standards of charity—namely, that an institution seeking tax-exempt status must serve a public purpose and not be contrary to established public policy." *Id.* at 586.

In a more recent case, *Green v. Bock Laundry Mach. Co.*, 109 S. Ct. 1981 (1989), the Court upheld a non-literal interpretation of Rule 609(a)(1) of the Federal Rules of Evidence where a strictly literal approach would lead to "an unthinkable disposition" and might render the Rule unconstitutional. *See id.* at 1994 (Scalia, J., concurring in the judgment).

In *Public Citizen v. United States Dep't of Justice*, 109 S. Ct. 2558 (1989), the Court rejected a literal application of a statute that would have led to the "outlandish" conclusion that Members

ensue from literal application of the market exclusivity provisions—granting the maximum economic reward to a drug that had to endure less than a maximum amount of regulatory delay and expense—does not seem likely to "defeat the plain purpose" of the statute, which was, after all, to strike a rough compromise between accelerating generic entry into the market and providing sufficient economic incentives for continued name-brand innovation.

That a statute yields a somewhat anomalous result does not mean that Congress could not have intended it. Many statutes, being products of innumerable and sometimes hasty and pragmatic compromises, permit seemingly arbitrary results. *See Board of Governors of the Federal Reserve Sys. v. Dimension Fin. Corp.*, 474 U.S. 361, 374 (1986). That fact is not cause, however, for rewriting them either in the agencies or in the courts. *See id.* Contrary to the tenor of the majority's analysis, Congress is not subject to the "arbitrary and capricious" constraints of the Administrative Procedure Act when it drafts and enacts statutes; and courts are not free to withhold enforcement of congressional enactments merely because they seem arbitrary or anomalous. *Cf. Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 n.9 (1983) (presumption of rationality accorded a statute is much greater than presumption of regularity accorded an agency action).

The majority labors mightily to discover a possible ambiguity in the statute in order to justify its refusal to adhere to the plain meaning of Congress' words. It concedes that Abbott's is the more obvious construction of the actual language used in the statute, but finds that reading unpalatable because of its suspicion that "Congress did not focus on the reverse sequence" problem.

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of Congress had intended to "subject[] their own political parties to bureaucratic intrusion and public oversight." *Id.* at 2566 n.9.

Judicial tinkering with statutes in order to correct suspected congressional oversights is, however, a dangerous business:

> In these rules [of statutory interpretation], we courts assume that Congress always knows the particulars whereof it speaks; we do not assert that as an empirical fact, for we all understand, as Horace said, that "sometimes even excellent Homer nods." We hold to this course, however, because there is no other less dangerous way; if courts were free to "correct" what they believe to be congressional oversights by construing unambiguous statutes to the contrary of their plain meaning—apart from that rare case in which specific legislative history compels such a result—even a good faith attempt to further Congress's goals would open the way to judicial hijacking of the power to legislate.

Consolidated Rail Corp. v. United States, 896 F.2d 574, 579 (D.C. Cir. 1990); *cf. Dow Jones & Co. v. Department of Justice*, 908 F.2d 1006, 1009 (D.C. Cir. 1990) (Silberman, J.) ("It may well be true that if Congress had thought about this question, the [statute] would have been drafted more broadly . . . . But Congress did not, and the words simply will not stretch to cover this situation . . . ."), *reh'g denied*, No. 89-5353 (D.C. Cir. Oct. 5, 1990).

There is nothing in the legislative history of the market exclusivity provisions to suggest the sort of "clearly expressed legislative intention to the contrary" that is normally required before a court will act to override a statute's plain meaning. *See Burlington Northern R.R. Co. v. Oklahoma Tax Comm'n*, 481 U.S. 454, 461 (1987) (quoting *United States v. James*, 478 U.S. 597, 606 (1986) (quoting *Consumer Prod. Safety Comm'n v. GTE Sylvania, Inc.*, 447 U.S. 102, 108 (1980))). Therefore, I cannot concur in the majority's decision to override the

words Congress chose to express its intention in this matter—particularly based upon judicial suspicion that Congress "did not focus" on a supposed anomalous eventuality that is, at any rate, without factual support in the record.

III.

Underlying the majority's analysis is the assumption that if one can perceive *any* ambiguity in a statute, however remote, slight or fanciful, the statute must be pushed into the second step of *Chevron* analysis, in which the court must defer to a reasonable agency interpretation. This fundamentally misconceives the point of *Chevron* analysis. *Chevron* does not suggest that courts are to search statutes, overturning linguistic rocks and brush, in the hope of discovering some arguable ambiguity, which would then justify deference to an administrative construction. The court's responsibility under the first step of *Chevron* analysis is considerably more serious: the court is to "employ[] traditional tools of statutory construction" to ascertain whether "Congress had an intention on the precise question at issue." *Chevron*, 467 U.S. at 843 n.9. Minor ambiguities or occasional imprecision in language may be brooked under *Chevron*'s first step, so long as "traditional tools of statutory construction" reveal Congress' intentions. *See NLRB v. United Food & Commercial Workers Union, Local 23*, 484 U.S. 112, 123 (1987) ("On a pure question of statutory construction, our first job is to try to determine congressional intent, using 'traditional tools of statutory construction.' If we can do so, then that interpretation must be given effect . . . ."). Advancement to *Chevron*'s second step is not appropriate merely where the court stumbles across a perceptible ambiguity; rather, given that the judiciary remains "the final authority on issues of statutory construction," *Chevron*, 467 U.S. at 843 n.9, abdication of that authority and deference to an administrative construction is legitimate only where the court confronts a

gap in the statute that cannot be bridged by way of traditional tools of statutory construction and which can properly be characterized as an express or implied delegation of authority by Congress to an agency, *see id.* at 843-44.

In this case, the majority has alerted upon a claimed ambiguity in the statute that apparently has occurred to no other reader—not to the District Court, not to Abbott, not to the agency charged with administering the statute and not to the Government's lawyers who appeared before this court on behalf of the agency. But the majority's announcement that it can perceive an ambiguity in the statute is alone not grounds for bucking the whole business back to the agency. The real question is whether, notwithstanding some arguably emprecision in language, Congress' intentions cannot be satisfactorily discerned from the terms of the statute. *See K Mart Corp. v. Cartier, Inc.*, 486 U.S. 281, 291 (1988) ("In ascertaining the plain meaning of the statute, the court must look to the particular statutory language at issue, as well as the language and design of the statute as a whole."). Indeed, to accept the majority's proposition that *Chevron* step-one analysis is finished as soon as a court can perceive *some* ambiguity in a statute would mean that all statutes must be analyzed under *Chevron*'s deferential second step, for clever lawyers—and clever judges—will always be capable of perceiving *some* ambiguity in any statute, no matter how clearly Congress struggles to emblazon its intentions on the face of the statute. That is clearly not what the Supreme Court intended in *Chevron* and it would hardly leave the judiciary, in any meaningful sense, as "the final authority" on issues of statutory construction. In *INS v. Cardozo-Fonseca*, 480 U.S. 421, 446-48 (1987), Justice Stevens (who wrote the opinion for the Court in *Chevron*) strongly indicates that the interpretation of a statutory provision remains "a pure question of statutory construction for the courts to decide"

even when the provision at issue admits of some ambiguity. Thus, the second step of the *Chevron* test is applicable only when a court is unable to discern congressional intent after employing traditional tools of statutory construction.

On the facts of this case, Congress' intention in the market exclusivity provisions is absolutely clear. "Active ingredient" is an unambiguous term of art and it does not include "active moiety." The agency's suggestion to the contrary flies in the face of the clear terms of the Act. Nor is there any genuine uncertainty about Congress' intention in the statute to refer to the active ingredient of the *new drug* for which market exclusivity is sought. The majority's discovery of a purported ambiguity in the statute's use of the articles "an" and "the" is at least as strained as the agency's finding of ambiguity in the word "including." Abbott is entitled to 10 years of market exclusivity for Depakote because neither its active ingredient, divalproex sodium, nor any ester or salt of divalproex sodium, has ever before been approved by the FDA.

Under *Chevron*, we are required to adhere to a statute's plain terms. Some courts have held that a statute's plain meaning may be ignored if there is a clear direction to the contrary in the legislative history or if strict adherence would defeat the clear purpose of Congress. However, neither possible exception applies in this case. Therefore, I would reverse the judgment of the District Court and apply the statute's plain terms in Abbott's favor.

APPENDIX B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 88-0474-OG

ABBOTT LABORATORIES,
Plaintiff,

v.

DR. FRANK E. YOUNG,
Commissioner, Food and Drug Administration,
Defendant.

Counsel:

For plaintiff: Harold D. Murry, Bryan Jay Yolles, Washington, D.C.

For defendant: Jeffrey Freedman, Associate Chief Counsel, Food and Drug Administration, Washington, D.C.; Jacqueline H. Eagle, U.S. Department of Justice, Washington, D.C.

MEMORANDUM

INTRODUCTION

Before the Court are two post-judgment motions. First, defendant, the Commissioner of the Food and Drug Administration ("FDA"), moves the Court to alter, in part, its memorandum filed July 25, 1988. Specifically, the FDA is concerned with the Court's finding that the term "active ingredient" must be ascribed consistent meanings in 21 U.S.C. § 355(j)(4)(D) (the provisions of the Hatch-Waxman Amendments to the Federal Food, Drug, and

Cosmetic Act which deal with marketing exclusivity) and in 21 U.S.C. § 355(j)(2)(A) (the abbreviated new drug application process provisions of the Amendments).[1]

Also before the Court is the motion of plaintiff Abbott Laboratories ("Abbott") for an order which would require the FDA to provide the Court and Abbott thirty days' notice before approving any generic copies of Abbott's prescription anticonvulsant, Depakote. "Abbott further moves that, in the event such notice is provided, the Court enter a preliminary injunction against such approvals pending entry of final judgment in this case and for thirty days thereafter." Motion for Order Requiring Prior Notice of FDA Approval of Generic Divalproex Sodium, and for Preliminary Injunction ("Plaintiff's Motion for Order") at 1-2. Because defendant's memorandum in opposition to plaintiff's motion raises a jurisdictional challenge to plaintiff's motion, plaintiff renews its motion pursuant to Rules 60(b)(6) and 62(c) of the Federal Rules of Civil Procedure. In the alternative, plaintiff moves the Court for an order enjoining the defendant, pending appeal, from making effective any approvals of generic copies of the drug Depakote.

BACKGROUND

This case was brought by Abbott after the FDA determined that Abbott's drug Depakote was entitled to only two years of marketing exclusivity instead of the ten years which Abbott contended was provided by the relevant statutory provisions. In its review of the FDA's decision, this Court made four findings. First, the Court held that the FDA did not abrogate the procedural requirements mandated by the Administrative Procedure

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[1] The dispute in this case involves the interpretation of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, as amended by the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, § 101, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355), which are known as the "Hatch-Waxman Amendments."

Act ("APA"), 5 U.S.C. §§ 701-706. Accordingly, the Court found that *de novo* review of the FDA's decision would be inappropriate. Court's Memorandum dated July 25, 1988 ("Court's Memorandum") at 9-13. Second, the Court found that the FDA's finding that divalproex sodium is a salt of valproic acid was not arbitrary and capricious.[2] Court's Memorandum at 13-15.

Third, the Court rejected the FDA's contention that contradictory definitions of the term "active ingredient" in the abbreviated new drug application provisions and in the exclusive marketing provisions are necessary to fulfill the distinct purposes of those two subsections of the Hatch-Waxman Amendments; the Court did not rule as to which definition should be adopted. *See* Court's Memorandum at 15-20. It is the Court's third finding which is the primary focus of the FDA's motion to alter or amend. Fourth, the Court determined that Depakote is entitled to two years of marketing exclusivity regardless of the definition of active ingredient.

DISCUSSION

I. *FDA's Motion to Alter*

The FDA contends that although the Court's third "conclusion is not the holding of the opinion and thus would not bind the agency," Defendant's Memorandum in

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[2] The parties in this matter disagree about what is the "active ingredient" in the drug Depakote. Abbott previously marketed the drug Depakene; the parties agree that the active ingredient in Depakene is valproic acid. Depakote, on the other hand, is administered as divalproex sodium. However, when this drug enters the disgestive system, it is converted into valproic acid. Although the parties agree that the pharmacologically active component (active moiety) of Depakote is valproic acid, the parties disagree about what is the "active ingredient." The problem is essentially a definitional one. Abbott asserts that the "active ingredient" should be defined as the ingredient in the final dosage form of the drug. The FDA contends "active ingredient" means the active moiety in the context of § 355(j)(4)(D).

Support of Motion to Alter Memorandum ("Defendant's Memorandum") at 1, "the Court's finding would be influential in future cases and could seriously undermine the agency's ability to carry out its responsibilities under the Act." Defendant's Memorandum at 2. The FDA makes five arguments in support of its motion. First, the FDA argues that the "Court's interpretation is not commanded by the language of the two provisions . . . ." Defendant's Memorandum at 2. Second, FDA argues that its construction of the two phrases is consistent with its longstanding interpretations, which were understood and adopted by Congress when it enacted the Hatch-Waxman Amendments. Third, the FDA argues that its construction of the statutory phrases is based on FDA's expertise and is therefore entitled to deference. Fourth, the FDA asserts that the Court's interpretation could produce irrational consequences in the implementation of both the ten- and the two-year exclusivity provisions. Finally, the FDA argues that it will be put into the position of having to choose between permitting the marketing of new drugs whose safety and effectiveness were uncertain or making a determination as to whether a company made a "substantial investment" in a drug (a determination which FDA claims is outside its area of expertise).

The plaintiff's memorandum in opposition to defendant's motion to alter asserts that the issues raised in defendant's motion were raised previously before this Court and rejected. Plaintiff contends that a post-judgment motion pursuant to Rule 52(b) or Rule 59(e) of the Federal Rules of Civil Procedure is not to be used as a vehicle to relitigate matters which have already been decided. Although the case law permits a court to consider newly discovered evidence central to a court's disposition of a case, *see Southern Air Transport, Inc. v. American Broadcasting Companies, Inc.*, 678 F. Supp. 8 (D.D.C. 1988), no new evidence has been presented in this case.

The Court must deny the defendant's motion. A review of the Defendant's Memorandum demonstrates that the arguments, based on the construction of the language of the relevant statutory provisions, the legislative intent of the Hatch-Waxman Amendments and the deference which should properly be accorded to an FDA interpretation of the relevant statutes, were raised by defendants previously. Furthermore, a review of the Court's Memorandum demonstrates clearly that the Court considered each of these claims previously. Additionally, the Court gave full consideration to the implications of its decision in rejecting the FDA's argument that "contradictory definitions are necessary to fulfill the distinct purposes of the two subsections." Court's Memorandum at 18. The Court, however, was unwilling to accept the agency's contention that the same term must be imbued with contradictory meaning when the term is used in different subsections of a coordinated legislative scheme. *Id.* at 19.

Essentially, the Court adheres to its opinion of July 25, 1988. FDA's apprehension that if the term "active ingredient" is defined consistently throughout the statute it will be confronted with administrative problems is illusory. These problems can be resolved by examining closely the statute itself. When this is done, as the Court has done following the hearing in open court at which time both sides were given the opportunity of addressing this issue, the Court has reached the following conclusion. The structure and language used in section 355(j) demonstrates a clear intent that the term "active ingredient" be defined consistently throughout section 355(j). The clearest manifestation of this intent is present in section 355(j)(7), which provides:

> For purposes of this subsection [*i.e.*, 355(j)]:
>
> > (A) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absor[b]ed from a

> drug and becomes available at the site of drug action.

21 U.S.C. § 355(j)(7)(A). Congress intended this definition of "bioavailability" to be applicable throughout section 355(j). For example, the term "bioavailability" appears in section 355(j)(2)(B). Congress intended for section 355(j)(7) to govern its interpretation. No other construction is reasonable. It follows, therefore, that the term "active ingredient," which is an integral part of the definition of the term "bioavailability," should be used consistently throughout section 355(j). Indeed, if the term "active ingredient" could be defined in different ways within section 355(j), the result would be that the term "bioavailability," in turn, could have two different definitions in the same statutory provision. Accordingly, the Court holds that Congress intended that the term "active ingredient" should have a consistent meaning throughout section 355(j).

In the Court's previous memorandum, in Part C the Court reviewed the legislative history of the Hatch-Waxman Amendments. The Court found that "neither the Amendments nor the legislative history reveals any congressional [intent] to imbue with contradictory meaning the term 'active ingredient' as used in the abbreviated new drug application [provisions] . . . and exclusive marketing provisions . . . of the Amendments." Court's Memorandum at 18. The Court concluded:

> Both subsections are part of a coordinated legislative scheme designed to foster these competing interests [of the benefit of increased availability of generic drugs and the need for continued research for the development of proven drugs]. Rather than being different, their purposes are complementary. In the absence of an express congressional purpose, the Agency's diametrically conflicting interpretations of "active ingredient" cannot be accepted.

Court's Memorandum at 19. Upon review of the legislative history, the Court reaffirms its prior conclusion that "active ingredient" must be defined consistently within section 355(j). Under the *in pari materia* doctrine, the Court finds that section 355(j)(4)(D) and section 355(j)(7) both relate to the same subject or object. *See Common Cause v. FEC*, 842 F.2d 436, 441-42 (D.C. Cir. 1988). Accordingly, the term "active ingredient" must be defined consistently throughout section 355(j).[3]

The legislative history and the structure of the statute support this interpretation. The Drug Price Competition and Patent Term Restoration Act contains two separate titles. "The purpose of Title I . . . is to make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962." H.R. Rep. No. 857, 98th Cong., 2d Sess., pt. 1, at 14 (1984) ("House Report"). The legislative history reflects that Title II had a different, albeit related, purpose. "The purpose of Title II of the bill is to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket government approval." House Report at 15. Sections 355(j)(4)(D) and 355(j)(7)(A) are both contained in Title I.

Plaintiff is correct in asserting that a post-judgment motion for reconsideration is not a vehicle for allowing a party to relitigate matters which have been decided. Accordingly, the defendant's motion to alter or amend must be denied.

Because the Court is cognizant of the important public policy implications of its decision, and because the Court

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[3] The Court did not hold that the term "active ingredient" must be equated with the broader term "active ingredient (including any ester or salt of the active ingredient)"; the Court holds only that "active ingredient" must be defined consistently throughout section 355(j).

finds that the FDA's motion is premised on an erroneous understanding of this Court's prior decision, the Court finds it appropriate to clarify the meaning of its earlier decision. The Court's previous holding does not require the FDA to *equate* the terms "active ingredient" and "active ingredient (including any ester or salt of the active ingredient)." The Court required only that the FDA must *define consistently* the underlying term "active ingredient" within the context of 21 U.S.C. § 355(j).

Thus, it may be an entirely reasonable construction of the statute for the FDA to interpret the statutory language "active ingredient (including any ester or salt of the active ingredient)" as evincing a legislative intent to include a broader class of chemical compounds than the more simple expression "active ingredient." Indeed, that Congress chose to include the parenthetical clarification in the former case may support this interpretation. The Court's July 25, 1988 decision does not preclude this interpretation.

The Court determined only that the term "active ingredient" must be interpreted consistently throughout section 355(j). Thus, the FDA cannot define "active ingredient" as "final dosage form" in one subsection of section 355(j), and define "active ingredient" as "active moiety" in a separate subsection of section 355(j). As the Court noted previously "in the absence of an express congressional statement or other evidence of congressional purpose, the Agency's *diametrically conflicting interpretations* of 'active ingredient' cannot be accepted." Court's Memorandum at 19.

II. *Abbott's Motion for Order Requiring Notice*

Abbott moves the Court for an order requiring the FDA to provide the Court and Abbott thirty days' notice before approving any generic copies of Abbott's drug Depakote. Apparently to clarify the jurisdictional basis

of its motion, Abbott filed a "renewed motion" indicating that the requested relief is sought pursuant to Rules 60 (b) and 62(c) of the Federal Rules of Civil Procedure. Abbott, in the alternative, moves for an order enjoining the defendant, pending appeal, from making effective any approvals of generic copies of the drug Depakote.

FDA argues that Abbott does not qualify for relief under Rule 60(b)(6).[4] First, the FDA asserts that Rule 60(b) is not a vehicle for relitigation of the merits of the case. Furthermore, the FDA argues that, although Rule 60(b)(6) provides relief for "any other reason justifying relief," Abbott has not set forth any such reason.

The FDA also contends that Abbott's request for pre-approval notice constitutes a new cause of action. Additionally, FDA argues that Abbott's request for preliminary injunctive relief is not ripe for review. Opposition to Plaintiff's Motion for Order at 6-7.

The Court finds that Abbott's motion is not properly before this Court. The issues raised in Abbott's motion bear no relation to the issues presented by defendant's motion to alter, which is the only matter presently pending before this Court. To the extent that the relief sought by Abbott was within the scope of the declaratory and injunctive relief sought in Abbott's original complaint, the Court finds that relitigation of issues which have been decided is not proper under Rule 60(b). *See Mastini v. American Telephone and Telegraph Co. v. New York Telephone Co.*, 369 F.2d 378, 379 (2d Cir. 1966), *cert. denied*, 387 U.S. 933 (1967). On the other hand, to the extent Abbott's request for relief presents questions which

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[4] The FDA also argues that Abbott's motion is not proper under Rule 59(e) or Rule 60(b)(1)-(5). Memorandum of Points and Authorities in Opposition to Plaintiff's Motion for Order ("Opposition to Plaintiff's Motion for Order") at 3-6. Abbott, however, does not claim it is entitled to relief pursuant to these provisions.

have not been raised previously before this Court, Abbott's request constitutes a new cause of action.[5] In either event, Abbott's motion is not properly before the Court.

III. *Abbott's Motion, in the Alternative, for an Injunction Pending Appeal*

The Court must also deny Abbott's motion in the alternative for an order, pursuant to Rule 62(c) of the Federal Rules of Civil Procedure, to enjoin the defendant, pending appeal, from making effective any approvals of generic copies of Abbott's drug Depakote. To afford Abbott such relief would require the Court effectively to grant Abbott a stay pending appeal. "In deciding whether to grant a stay pending appeal, the Court must consider whether the moving party is likely to prevail on the merits of his appeal, whether, without a stay, the moving party will be irreparably injured, whether the issuance of a stay will substantially harm other parties interested in the proceeding, and, finally, wherein lies the public interest." *Hammerman v. Peacock*, 623 F. Supp. 719, 721 (D.D.C. 1985). Application of this standard to the facts of this case requires denial of Abbott's motion.

Obviously, the Court finds it unlikely that Abbott will prevail on the merits of its appeal; otherwise, the Court would not have granted summary judgment in defendant's favor. The Court also finds the other factors compel denial of Abbott's motion.

The Court finds no apparent irreparable injury which will befall Abbott in the absence of a stay. Although some

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[5] In its original complaint, Abbott sought *de novo* review of FDA's factual findings and declaratory and injunctive relief reversing the FDA's resolution of issues against it. If Abbott were to file a new case, the threshold question of whether the action was barred by res judicata would necessarily be raised. That issue, however, has not been briefed by the parties. Accordingly, the Court declines to decide that question at this stage.

economic injury to Abbott could occur if Abbott subsequently was found to be entitled to ten years of exclusive marketing, this injury does not appear to be irreparable. *See Wisconsin Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985) (per curiam) (it is well settled that economic loss does not, in and of itself, constitute irreparable harm).

The Court also finds that potential harm to third parties and the public interest compel denial of Abbott's motion for a stay. Other drug manufacturers may be harmed if Abbott is effectively granted a greater period of exclusive marketing than that to which Abbott is legitimately entitled under the statute. Additionally, the public interest in making available lower-cost generic substitutes of Depakote would be inhibited by a stay in this case.[6] Accordingly, Abbott's motion must be denied.

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[6] The Court finds Abbott's argument that the public interest favors an injunction to be unpersuasive. Abbott points out that if a generic equivalent became available and was subsequently withdrawn, patients taking a generic equivalent of Depakote could be adversely affected. In support of its position, Abbott offers the affidavits of three physicians which substantiate the assertion that switching medications in epileptic patients, even from a brand-name of a drug to a generic equivalent, can adversely affect an epileptic patient's status. *See* Exhibits B, C, and D, appended to Plaintiff's Memoradnum of Points and Authorities in Support of Motion for Order Requiring Prior Notice of FDA Approval of Generic Divalproex Sodium and for Preliminary Injunction.

Abbott's argument appears to overlook the fact that Depakote will remain available on the market even in the event a generic equivalent is approved by the FDA. Furthermore, any patient taking Depakote will necessarily be doing so under the guidance of a licensed physician. Simply because the FDA may approve a generic equivalent of Depakote does not necessarily mean that any physician will switch his or her patients to the generic equivalent if doing so would present an inherent risk to the patient's well-being. Any threat to the public interest, therefore, is purely conjectural.

CONCLUSION

The Court finds that all pending motions must be denied. Defendant's motion to alter the Court's memorandum must be denied because the Court has previously considered all of the arguments presented by defendant; a post-judgment motion for reconsideration is not a vehicle to permit a party to relitigate matters which have been decided.

Plaintiff's motion for an order requiring notice must be denied as well, since the motion is not properly before the Court. To the extent that the relief Abbott seeks was sought in its original complaint, this motion attempts to relitigate issues which have already been decided. To the extent Abbott's motion presents questions which have not been raised previously before this Court, Abbott's motion introduces a new cause of action. The Court also finds that Abbott's motion, in the alternative, for an injunction pending appeal must be denied. The Court finds that Abbott has not demonstrated a likelihood of success on the merits of its appeal, nor has Abbott demonstrated that irreparable injury will result in the absence of a stay. The Court also finds that potential harm to other drug manufacturers, as well as the public interest, compel denial of plaintiff's motion.

/s/ Oliver Gasch
Judge

Date: June 22nd 1989

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 88-0474-OG

ABBOTT LABORATORIES,
Plaintiff,

v.

DR. FRANK E. YOUNG, Commissioner,
Food and Drug Administration,
Defendant.

ORDER

Upon consideration of defendant's motion to alter the Court's memorandum and plaintiff's motion for an order requiring prior notice of FDA approval of generic divalproex sodium, and for preliminary injunction and plaintiff's renewed motion for relief or, in the alternative, for injunction pending appeal, and for expedited consideration, the memoranda in support thereof and in opposition thereto, the arguments presented by counsel in open court, the entire record herein, and for the reasons stated in the accompanying memorandum, it is by the Court this 22nd day of June, 1989,

ORDERED that defendant's motion to alter the Court's memorandum be, and hereby is, denied; and it is further

ORDERED that plaintiff's motion for an order requiring prior notice of FDA approval of generic divalproex sodium, and for preliminary injunction and plaintiff's renewed motion for relief, or in the alternative, for injunction pending appeal, and for expedited consideration be, and hereby are, denied.

/s/ Oliver Gasch
Judge

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 88-0474-OG

ABBOTT LABORATORIES,
Plaintiff,

v.

DR. FRANK E. YOUNG, Commissioner,
Food and Drug Administration,
Defendant.

Counsel:

For plaintiff:

Harold Murry, Bryan Yolles and
Robert Reznick of Clifford &
Warnke, Washington, D.C.

For defendant:

Jacqueline Eagle, Department of
Justice, Washington, D.C.

MEMORANDUM

[Filed Jul. 25, 1988]

Aggrieved by certain informal action taken by the Food and Drug Administration ("FDA" or "Agency"), plaintiff Abbott Laboratories ("Abbott") seeks *de novo* review of the Agency's factual findings and declaratory and injunctive relief reversing the Agency's resolution of pertinent legal issues. Abbott seeks this judicial re-

view under the Administrative Procedure Act ("APA"). 5 U.S.C. §§ 701-706. The focus of the factual and legal disputes is the Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, as amended by the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, § 101, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355) which are commonly referred to as the Hatch-Waxman Amendments.

I. *BACKGROUND*

On February 28, 1978, the FDA approved a new drug application submitted by Abbott for the drug Depakene, an anti-convulsant drug indicated for patients, including epileptics, who suffer various kinds of seizures. The therapeutic ingredient in Depakene is valproic acid, and the drug is administered as a syrup or a soft-gelatin tablet. Taken in this form, the drug frequently causes gastrointestinal side-effects.

In 1981, Abbott began investigating a new anticonvulsant drug, Depakote, that is formulated as a specially coated table. In this form, the drug does not dissolve in the stomach and does not cause the undesirable side-effects common with Depakene. In order to develop this improved anticonvulsant, Abbott replaced valproic acid—the ingredient in Depakene—with divalproex sodium. When this chemical enters the digestive system it is converted into valproic acid. *See* Depakote New Drug Application, *reproduced in* Administrative Record at 314 [hereinafter A.R.]. Thus, Depakote achieves the same pharmaceutical effect as Depakene.

Later in 1981, Abbott submitted a new drug application for Depakote ("Depakote NDA"). Because the pharmaceutically active chemical in Depakote is identical to that in Depakene, Abbott requested that the FDA refer to the Depakene application for the required clinical studies of safety and efficacy. Letter from A. G. Ramsay, Ab-

bott Laboratories, to Bureau of Drugs (Dec. 29, 1981) (transmitting Depakote NDA), *reproduced in* A.R. at 310; Depakote New Drug Application, *reproduced in* A.R. at 321-324. The primary clinical studies conducted by Abbott were simply to demonstrate that recommended dosages of Depakote did yield biologically equivalent amounts of Depakene's active ingredient, valproic acid. Abbott successfully demonstrated the therapeutic equivalence of Depakote and Depakene, and the Depakote NDA was approved on March 10, 1983. *See* Letter from Robert J. Temple, M.D., National Center for Drugs and Biologics, to E.B. Chappell, Abbott Laboratories (March 10, 1983), *reproduced in* A.R. at 294.

One and one-half years after Depakote received FDA approval, Congress enacted the Hatch-Waxman Amendments. Among the purposes of the Amendments was the enhancement of competition in the drug industry through abbreviated procedures for the approval of generic copies of approved drugs. *See Mead Johnson Pharmaceutical Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988); *see also* H.R. REP. NO. 98-857, 98th Cong., 2d Sess., pt. 1, at 14-15, *reprinted in* 1984 U.S. CODE CONG. & ADMIN. NEWS 2647, 2647-48 [hereinafter H.R. REP. NO. 98-857]. These procedures substantially shorten the time and expense incurred by drug manufacturers to obtain FDA approval of generic drugs. To protect the research and development investments of the pioneer drug industry, however, the Amendments also entitle various categories of drugs that are approved through the NDA process, 21 U.S.C. § 355(b), to exclusive marketing periods regardless of patent protection. This privilege "protects products whose development has taken much time and money in FDA testing and review, but which have little [or] no patent life left when they are finally allowed on the market." 130 CONG. REC. S10504 (Aug. 10, 1984) (statement of Sen. Hatch) [hereinafter Hatch Statement]. During the exclusive marketing period, no abbreviated

new drug application ("ANDA") may be approved for a generic copy of the NDA-approved drug. 21 U.S.C. § 355(j)(4)(D); *see* Hatch Statement, 130 CONG. REC. S10504; 130 CONG. REC. H9113-14 (Sept. 6, 1984) (statement of Rep. Waxman) [hereinafter Waxman Statement].

Following passage of the Hatch-Waxman Amendments, Abbott submitted "Patent and Exclusivity Information" for divalproex sodium, the active ingredient in the final dosage form of Depakote.[1] Letter from Martin L. Katz, Abbott Laboratories, to Thomas J. McGinnis, Food and Drug Administration (Oct. 23, 1984), *reproduced in* A.R. at 19-20. Abbott declared that divalproex sodium is entitled to ten years of exclusive marketing from March 10, 1983. Without further communication between the parties, FDA determined that the drug may be marketed exclusively by Abbott only for two years from the date of enactment of the Amendments—September 24, 1984. CENTER FOR DRUGS AND BIOLOGICS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, APPROVED DRUG PRODUCTS (6th ed. 1985) (complaint Ex. B) [hereinafter APPROVED DRUG PRODUCTS].

After Abbott objected to this designation, Letter from Michael Nelson, Abbott Laboratories, to Thomas J. McGinnis (July 10, 1986), *reproduced in* A.R. at 22-26, FDA affirmed its decision and suggested that Abbott might pursue its dissatisfaction by filing a citizen petition with the Commissioner of the FDA. Letter from Thomas J. McGinnis to Michael Nelson (Aug. 12, 1986), *reproduced in* A.R. at 27-28. Abbott heeded this advice and submitted such a petition, pursuant to 21 C.F.R. § 10.30, on August 29, 1986. In the petition, Abbott requested "a ruling that [its] drug product, DEPAKOTE (divalproex sodium), can be marketed exclusively by the

[1] The final dosage form of a drug is the form in which it appears prior to administration to the patient. Depakote is a tablet that contains divalproex sodium.

Company for ten years from . . . March 10, 1983."[2] Citizen Petition, Docket Number 86P-0367/CP (Aug. 29, 1986), *reproduced in* A.R. at 1 *et seq.* [hereinafter Citizen Petition]. The basis for Abbott's contention was one of two exclusive marketing provisions at issue in this case:

> If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the date of enactment of this subsection [September 24, 1984], the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b).

21 U.S.C. § 355(j)(4)(D)(i).[3] Abbott argued that the term "active ingredient" refers to the ingredient in the "final dosage form of the product . . . not the form the ingredient might take upon administration to the patient." Letter from Bryan Yolles, Counsel for Abbott Laboratories, to Ann Witt, Food and Drug Administration (Feb. 27, 1987), *reproduced in* A.R. at 139A-F. Based upon this interpretation of the statute, the company insisted that the "active ingredient" in Depakote is divalproex sodium and that neither this chemical nor a salt or ester of this chemical had previously been approved under the

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[2] Pursuant to 21 C.F.R. § 10.35, Abbott also petitioned the Agency for a stay of approval of any abbreviated new drug applications requesting permission to market generic copies of Depakote. Petition for Stay of Action (Aug. 29, 1986), *reproduced in* A.R. at 66-74.

[3] The extraordinarily dense language of this statute is parsed and explained below.

NDA procedures of section 355(b).[4] Accordingly, Abbott concluded that Depakote qualifies for ten years of exclusive marketing under section 355(j)(4)(D)(i).

In a decision rendered February 11, 1988, the FDA denied Abbott's petition. Letter from John M. Taylor, Associate Commissioner for Regulatory Affairs, to Bryan J. Yolles, *reproduced in* A.R. at 192 [hereinafter Agency Decision].[5] The foundation of the Agency's decision was the factual finding that divalproex sodium is "simply a salt of valproic acid." *Id.* at 2, A.R. at 194. The agency relied upon the "standard definition of salt," the "official rules of nomenclature for chemical compounds," and the affidavit of Dr. Robert H. Wood, a professor of chemistry at the University of Delaware. In Dr. Wood's view, the problem is one of nomenclature, and the rules applicable to salts classify divalproex sodium as a salt of valproic acid. *See* Affidavit of Robert H. Wood, PhD. ¶¶ 3-5, Exhibit A to Agency Decision, *reproduced in* A.R. at 213-15. The doctor rejected Abbott's attempts to distinguish divalproex sodium from other salts based on various physical and chemical properties of the substance. *Id.* ¶¶ 6-14, A.R. at 215-19.

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[4] In its citizen petition, as supplemented, Abbott cited a variety of scientific tests regarding the chemical and physical properties of divalproex sodium. The purpose of the tests was to demonstrate that divalproex sodium is a chemical entity distinct from valproic acid, the active ingredient in Depakene, and sodium valproate, the sodium salt of valproic acid. The company further argued that if divalproex sodium were a salt, it would be the salt of divalproic acid which had never previously been approved by the FDA. *See* Citizen Petition, A.R. at 14. Abbott also challenged the FDA's conclusions that divalproex sodium is a salt and that it is nothing more than a combination of valproic acid and sodium valporate. Second Supplement to Citizen Petition (Feb. 5, 1987), *reproduced in* A.R. at 115, 116, 119-122.

[5] The Agency contemporaneously denied Abbott's request for a stay of approval of ANDA's submitted for generic copies of Depakote. Agency Decision, A.R. at 193.

The FDA further reasoned that the congressional policy underlying the ten-year exclusive marketing provision is not served by qualifying Depakote under this provision because Abbott did not perform the extensive clinical studies for safety and efficacy usually required of NDA applicants. Instead, the Agency accepted the company's assertion in the Depakote NDA that the pharmaceutically active component of the drug—valproic acid—is identical to that found in Depakene. Thus, Abbott did not make the investment in time or money contemplated by Congress when it determined to include the exclusive marketing provisions in the Hatch-Waxman Amendments. *See* Agency Decision at 11-14, A.R. at 202-05.

Finally, the FDA rejected Abbott's definition of "active ingredient" as referring to the ingredient in the final dosage form of the drug. Rather, the Agency concluded that as used in sections 355(j)(4)(D)(i)-(v), "active ingredient" refers to the pharmaceutically active component (active moiety) of the drug. The active moiety in both Depakote and Depakene is valproic acid. The FDA relied on its perception of legislative policy underlying the exclusivity provisions to distinguish a broader definition of "active ingredient" applied as the term is used in section 355(j)(2)(A)(ii) which defines the types of drugs that are eligible for the abbreviated approval procedures. *Id.* at 14-16, A.R. at 205-07.

The Agency concluded that section 355(j)(4)(D)(v), a subsection of the exclusivity provisions not referenced by Abbott, requires that Depakote receive only two years of protection from competition from generic substitutes. That subsection states:

> If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982,

> and ending on the date of the enactment of this subsection [September 24, 1984], the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted . . . before the expiration of two years from the date of enactment of this subsection [September 24, 1984].

21 U.S.C. § 355(j)(4)(D)(v). Because the FDA concluded that the active ingredient in Depakote is valproic acid, which had previously been approved as an active ingredient in Depakene, it determined that Depakote was entitled only to two years of exclusivity.

II. *DISCUSSION*

On its face, the parties dispute raises a novel issue of statutory interpretation of the exclusivity provisions of the Hatch-Waxman Amendments. An undercurrent of argument focuses on the standards of review applicable under the APA to the FDA's interpretation of these provisions. A threshold issue, however, is presented by Abbott's complaint that the Agency relied heavily on evidence regarding which Abbott was not permitted an opportunity to comment.

A. *Abbott's Right To Comment Upon The Affidavit Of Dr. Robert H. Wood*

In response to a request from the FDA's Center for Drugs and Biologics, Abbott supplemented its citizen petition in February 1987 with evidence and analysis purporting to demonstrate that divalproex sodium is not a salt. Second Supplement to Citizen Petition (Feb. 5, 1987), *reproduced in* A.R. at 115. The supplement consisted of scientific data and an analysis of that data. Additionally, Abbott submitted affidavits of professors of Chemistry at Northwestern University and Purdue University. Exhibit C to Plaintiff's Cross-Motion for Sum-

mary Judgment [hereinafter Plaintiff's Cross-Motion].[6] From these data and affidavits, Abbott argued that divalproex sodium exhibits substantially different properties from valproic acid and sodium valporate. Exhibit A to Second Supplement to Citizen Petition, *reproduced in* A.R. at 119, 121. Moreover, Abbott's experts opined that the physical characteristics of divalproex sodium preclude categorization of the drug as a salt. Affidavit of Dr. Joseph B. Lambert ¶¶ 2-5 [hereinafter Lambert Affidavit]; Affidavit of Dr. Stephen R. Byrn ¶¶ 5-6 [hereinafter Byrn Affidavit].

Sometime after these submissions, the FDA solicited a rebuttal affidavit from Dr. Robert H. Wood. The affidavit addresses the categorization of divalproex sodium as an issue of nomenclature. Wood Affidavit ¶¶ 3-4, A.R. at 213-14. Based on the chemical structure of the drug, Dr. Wood concluded that according to well-accepted conventions of nomenclature, divalproex sodium is an acid salt of valproic acid. *Id.* ¶¶ 5-6, A.R. at 214-15. After reaching this conclusion, Dr. Wood considered Abbott's arguments regarding the physical properties of the drug. He asserted that these properties—high molecular weight, oligomeric structure, solubility, and low melting point—are irrelevant to the categorization of divalproex sodium as a salt. *Id.* ¶¶ 6, 9-14, A.R. 215-19.

In its reply in support of its cross-motion for summary judgment, Abbott complains that the affidavit of Dr. Wood was hidden from the company's scrutiny, though heavily relied upon by the FDA. Citing the notice and comment requirements of informal rule-making, 5 U.S.C. § 553(c), Abbott argues that the Agency's procedures were defective.

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[6] Although the affidavits are not found in the administrative record submitted to the Court, Abbott contends that the affidavits and curriculum vitae of the affiants were delivered to the FDA on February 11, 1987 and were accidentally omitted from the administrative record. FDA does not dispute this contention.

Specifically, the company insists that it was entitled to an opportunity to controvert Dr. Wood's opinion.

While an agency is required to disclose files or reports it deems relevant to the proceeding, *U.S. Lines, Inc. v. Federal Maritime Commission*, 584 F.2d 519, 534 (D.C. Cir. 1978), the process of agency fact-finding and deliberation cannot be interminable. The purpose of this disclosure requirement is to ensure that interested parties have a meaningful opportunity to participate in agency proceedings, *id.*, and that the Court has an adequate record from which to determine whether the agency properly performed its functions. *See Portland Cement Association v. Ruckelshaus*, 486 F.2d 375, 393-94 (D.C. Cir. 1973).

At the request of the FDA, Abbott submitted scientific data and expert opinion regarding the classification of divalproex sodium. Without collecting any additional data, the Agency solicited an additional expert opinion that refutes the conclusion of Abbott's experts. Abbott would have the Court rule that the FDA was obliged to permit the company to submit additional expert opinion regarding the nomenclature rules applicable to divalproex sodium. Neither *U.S. Lines* nor *Portland Cement* supports such a demand.

The Agency's request for additional information contemplated "evidence that [di]valproic acid exists as a chemical entity distinct from valproic acid; and . . . information on the properties of related substances having ratios of valproic acid to such metals as sodium, potassium, and calcium." Letter from Ann M. Witt to Bryan Yolles (Jan. 16, 1987), *reproduced in* A.R. at 114. In response, Abbott submitted data and a memorandum purporting to demonstrate that divalproex sodium "is a chemical entity distinct from valproic or sodium valproate; is not a combination or mixture of valproic acid and sodium valproate; and is not a salt; and specifically not a salt

of valproic acid." Second Supplement, A.R. at 116; *see* Lambert Affidavit; Bryn Affidavit. The Wood affidavit simply offered an opinion that divalproex sodium is a salt of valproic acid. The opinion was based on conventions of nomenclature well-known to Abbott's experts.

Neither fairness nor the needs of the reviewing Court required that Abbott be allowed to submit further opinion to which the FDA would inevitably desire to respond. Because the Agency did not abrogate procedural requirements, *de novo* review by the Court would be inappropriate. *See Environmental Defense Fund, Inc. v. Costle*, 675 F.2d 275, 284-85 (D.C. Cir. 1981). Similarly, remand to the Agency is not required unless the Court finds that the factual finding—that divalproex sodium is a salt of valproic acid—was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *see Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 414 (1971) (judicial review of informal rulemaking is conducted under section 706(2)(A)).[7]

B. *The FDA's Finding That Divalproex Sodium Is A Salt Of Valproic Acid Was Not Arbitrary And Capricious*

While the parties agree in principle that judicial review in this case must be conducted under the "arbitrary and capricious" standard, their elaboration of that

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[7] Abbott's complaint also suggests that the FDA's action on the citizen petition was "short of statutory right," 5 U.S.C. § 706(2)(C). Complaint ¶ 26. Abbott cites no provision of the Hatch-Waxman Amendments that limits the power of the FDA to make factual findings essential to determining the duration of marketing exclusivity to which a drug is entitled. Presumably, Abbott is referring to its contention that section 355(j)(4)(D)(i) authorizes ten years of exclusivity for Depakote. If Abbott is correct, the Agency's conclusion to the contrary will have been contrary to law. Thus, the standard set forth in section 706(2)(C) is in this case duplicative of that stated in section 706(2)(A).

standard varies markedly. It is well-settled, however, that "[t]he scope of review . . . is narrow and a court is not to substitute its judgment for that of the agency. . . . [T]he agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" *Motor Vehicle Manufacturers Association v. State Farm Mutual Automobile Insurance Co.*, 463 U.S. 29, 43 (1983); *see Eagle-Picher Industries v. E.P.A.*, 759 F.2d 905, 921 (D.C. Cir. 1985). Much deference is accorded the agency, and its action is presumed to be valid. *See United Transportation Union v. Lewis*, 711 F.2d 233, 252 (D.C. Cir. 1983) (citing *Overton Park*, 401 U.S. at 415). Deference is particularly advised when the administrative action is based on the expertise of the agency. *See Baltimore Gas and Electric Co. v. Natural Resources Defense Council, Inc.*, 462 U.S. 87, 103 (1983); *Community Nutrition Institute v. Young*, 773 F.2d 1356, 1363 (D.C. Cir. 1985) ("court will not substitute its judgment on highly technical and factual matters for that of the [FDA which is] charged with the supervision of the industry"). Nevertheless, the Court's inquiry into the administrative record must be " 'searching and careful' . . . to ensure that the agency's decision was a product of reasoned decisionmaking based upon a consideration of relevant factors." *Motor Vehicle Manufacturers Association v. E.P.A.*, 768 F.2d 385, 389 n.6 (D.C. Cir. 1985) (citing *Small Refiners Lead Phase-Down Task Force v. E.P.A.*, 705 F.2d 506, 520 (D.C. Cir. 1983)).

The FDA's determination that divalproex sodium is a salt of valproic acid falls well within the bounds of reasoned decisionmaking. The Agency was presented with authoritative but conflicting opinions regarding the appropriate basis for classification of salts. After considering the distinctions drawn by Abbott's experts, the FDA reasonably concluded that classification should be based on known standards of nomenclature. At the same time, it

noted that Abbott's attempt to exclude divalproex sodium from classification as a salt was based on physical properties of the drug that are irrelevant to classification. Agency Decision at 6, A.R. at 197. Further, the Agency reasonably declined to adopt Abbott's method for classifying salts because it was not based on any definition of salt but a weighing of the similarities of a drug to "typical salts." *Id.* Such a method would be far less predictable and manageable than the nomenclature method. Accordingly, the Court declines to second-guess the scientific expertise of the FDA and concludes that the Agency's classification of divalproex sodium as a salt was not arbitrary or capricious.

C. *The FDA's Definition Of "Active Ingredient" As Used In Section 355(j)(4) Of The Hatch-Waxman Amendments*

Essential to application of the marketing exclusivity provisions of the Hatch-Waxman Amendments is the definition of the term "active ingredient." Abbott argues that the term refers to the ingredient as it exists in the final dosage form of the product; that is, the form the product takes prior to ingestion by the patient. Letter from Bryan Yolles, Counsel for Abbott Laboratories, to Ann Witt, Food and Drug Administration (Feb. 27, 1987), *reproduced in* A.R. at 139A-F. Conversely, the FDA has stated that it believes the term applies to the pharmaceutically active ingredient (active moiety) of the drug.

In this case, the dispute is whether the active ingredient is divalproex sodium—the ingredient that appears in the final dosage form of depakote—or valproic acid—the chemical that yields the therapeutic effect. The disagreement is material to application of the marketing exclusivity provisions of the Amendments. As the discussion below explains, Abbott's definition leads to irreconcilable results while the FDA's definition is inconsistent with a

definition assigned to the same term as used in section 355(j)(2).

The marketing exclusivity provisions at issue in this case are an element of a coordinated legislative effort to streamline administrative procedures for the approval of generic drugs. *See Mead Johnson*, 838 F.2d at 1333; H.R. REP. NO. 98-857 at 14-15, 1984 U.S. CODE CONG. & ADMIN. NEWS at 2647-48. To qualify for the abbreviated new drug application process, a drug must have the same active ingredients as the drug of which it is a copy. 21 U.S.C. §§ 355(j)(2)(A)(ii) & (j)(2)(A)(iii). On several occasions, the FDA has determined a drug to be ineligible for the ANDA process because this requirement was not satisfied. In making this determination, the Agency has stated that "[t]he term active ingredient in the Act refers to the active ingredient *found in the final dosaage form prior to the administration of* [*the*]*product to the patient*, rather than to any resultant form the drug may take following administration." Letter from Dr. Peter H. Rheinstein, Center for Drugs and Biologics, to I.R. Berry, Pharmacaps, Inc. (Feb. 13, 1986) (emphasis added), *reproduced in* A.R. at 30; Letter from Dr. Peter H. Rheinstein to George W. Severn, Rowell Laboratories, Inc. (June 5, 1986), *reproduced in*, A.R. at 36. Abbott asserts that the same definition should apply to the term as used in sections 355(j)(4)(D)(i)-(v). The FDA disagrees.

In its decision denying Abbott's citizen petition, the FDA stated:

> Abbott's interpretation is [not] consistent with Congressional intent, nor is it mandated by FDA's interpretation of "same active ingredient" for purposes of permitting the marketing of new drug products through abbreviated applications. This interpretation of "same active ingredient" is inapplicable to the agency's determination of the period of exclusivity

> for which Depakote qualifies, on two independent grounds. First, as already explained, Depakote is a salt of an already approved active ingredient and thus does not fall within the plain language of eligibility for the exclusivity provisions at issue. Second, neither the language of, nor the policies underlying, the exclusivity provisions are the same as those of the ANDA eligibility provisions in section 505(j)(2)(C).

Agency Decision at 14-15, A.R. at 205-06. The first of the Agency's "grounds" for adopting an inconsistent definition of "active ingredient" defies understanding. At best, the explanation simply begs one of the legal issues about which the parties disagree. The second ground recites fundamental principles of statutory interpretation.

Because definition of "active ingredient" demands interpretation of the Hatch-Waxman Amendments, the first question is "whether Congress has directly spoken to the precise question at issue." *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842 (1984).

> If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress. If, however, the court determines that Congress has not directly addressed the precise question at issue, the court does not simply impose its own construction on the statute, as would be necessary in the absence of an administrative interpretation. Rather, if the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute.

Id. at 842-43 (footnotes omitted). As with the arbitrary and capricious standard, deference to the agency is appropriate, and "[t]he agency's construction is adequate if it

falls within the permissible range of interpretations." *Office of Consumers' Counsel v. F.E.R.C.*, 783 F.2d 206, 218 (D.C. Cir. 1986).

Following *Chevron U.S.A.*, the Court notes that neither the Amendments nor the legislative history reveals any congressional desire to imbue with contradictory meaning the term "active ingredient" as used in the abbreviated new drug application, 21 U.S.C. § 355(j)(2)(A), and exclusive marketing provisions, *id.* § 355(j)(4)(D), of the Amendments. Thus, in the context of this case, the inquiry is whether the FDA reasonably offers contradictory definitions of "active ingredient" for two subsections of the same section of the Hatch-Waxman Amendments. The Agency argues that the contradictory definitions are necessary to fulfill the distinct purposes of the two subsections. As used in the ANDA subsection, "active ingredient" must be construed narrowly to ensure that the abbreviated approval procedures are not applied to drugs that are not truly the same as previously approved drugs. With respect to the exclusive marketing subsection, however, the Agency perceives a congressional intent to define broadly the term "active ingredient" in order to restrict the exclusive marketing privilege to those drugs that are genuinely new chemical entities.

Although the FDA may state a logical policy for the application of the subsections at issue, that policy is entirely an invention of the Agency. Moreover, it does not reflect a judgment based on the expertise of the Agency; instead, it is a uniquely legislative evaluation of the benefit of increased availability of generic drugs and the need for continued research for the development of pioneer drugs. Both subsections are part of a coordinated scheme designed to foster these competing interests. Rather than being different, their purposes are complementary. In the absence of an express congressional statement or other evidence of congressional purpose, the Agency's diametri-

cally conflicting interpretations of "active ingredient" cannot be accepted. *See Barnson v. U.S.*, 816 F.2d 549, 554 (10th Cir. 1987); *Firestone v. Howerton*, 671 F.2d 317, 320 (9th Cir. 1982); *cf. Laffey v. Northwest Airlines, Inc.*, 567 F.2d 429, 461, n.230 (D.C. Cir. 1976) (same term in civil and criminal sections given different meaning because civil section had no punitive purpose). Such statutory construction simply is unreasonable.[8]

Given this disposition of the FDA's conflicting definitions of "active ingredient," the question necessarily arises whether the definition espoused in the Agency's ANDA opinions will prevail or the broader definition proffered in this case will be adopted. Although the Court cannot be certain which the FDA will prefer, the choice is irrelevant in this case.

D. *Regardless Of The Definition Of Active Ingredient, Depakote Is Entitled To Two Years Of Marketing Exclusivity*

With the several peripheral and threshold issues resolved, the Court turns to the focus of the parties' arguments—the exclusive marketing provisions. Simply stated, the question is whether subsection (i) or subsection (v)

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[8] The FDA's narrow definition of "active ingredient" as used in the ANDA provision is also inconsistent with Congress' decision to reject a definition that required identity between the ingredients in the generic drug and the drug being copied.

> Some have suggested that a generic drug must be identical in all respects to the listed drug instead of the same. The regulations that permit ANDA's for pre-1962 pioneer drugs make no such distinction. In rejecting the use of the term identical, the FDA regulation comments that "identical means a product that is the same in dosage form, strength, and route of administration, contains the same active ingredient, and is recommended for use under the same conditions of use." The Committee has adopted the FDA's policy of utilizing the term "same" . . . .

H.R. REP. NO. 98-857, at 21, 1984 U.S. CODE CONG. & ADMIN. NEWS at 2654 (footnotes omitted).

of 21 U.S.C. § 355(j)(4)(D) applies to Abbott's product Depakote. Subsection (i) provides:

> If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the date of enactment of this subsection [Setember 24, 1984], the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b).

Recast in comprehensible language, this subsection provides that a drug that was approved between January 1, 1982 and September 24, 1984 by the FDA pursuant to the complete new drug application procedure is entitled to ten years of protection from competition by generic copies if neither the active ingredient of that drug, the salt of the active ingredient, nor the ester of the active ingredient had previously been approved by the FDA. Abbott asserts that its new drug Depakote has divalproex sodium as its active ingredient and that neither this ingredient, a salt of it, nor an ester of it had previously been approved by the FDA.[9] The FDA contends that the active ingredient in Depakote is valproic acid. As Abbott admits, valproic acid is the active in-

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[9] The Court is disquieted with this argument given the conclusion above that divalproex sodium is a salt of valproic acid. This fact, however, is irrelevant to application of subsection (i). The question under this subsection is whether the active ingredient or a salt or ester of it had previously been approved, not whether the active ingredient is a salt or ester of a previously approved drug. Though this construction of the subsection seems incomplete, the plain language of the statute allows no other.

gredient in Depakene which was approved by the FDA approximately two years before Depakote. If the Agency is correct, subsection (i) does not apply to Depakote, and Abbott is not entitled to ten years of exclusive marketing of Depakote.

The other subsection of the exclusive marketing provisions that is implicated by the parties' dispute is subsection (v) which states:

> If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved the period beginning January 1, 1982, and ending on the date of the enactment of this subsection [September 24, 1984], the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted . . . before the expiration of two years from the date of enactment of this subsection [September 24, 1984].

Restated, the subsection allowed exclusive marketing until September 24, 1986 to a drug that was approved pursuant to the complete new drug application process and that contains an active ingredient or the salt or ester of an active ingredient that had previously been approved by the FDA. Assuming, as Abbott would like, that divalproex sodium is the active ingredient in Depakote, subsection (v) requires that the drug received only two years of exclusive marketing rights because divalproex sodium is a salt of valproic acid. As noted above, however, when subsection (i) is applied with divalproex sodium as the active ingredient, Depakote is entitled to ten years of exclusive marketing. Thus, if Abbott is correct that divalproex sodium is the active ingredient in Depakote, an irreconcilable statutory conflict arises.

The FDA's identification of valproic acid as the active ingredient of Depakote avoids this conflict. As already noted, subsection (i) does not apply to Depakote if its active ingredient is deemed to be valproic acid. Subsection (v), however, would apply because Depakote was approved under the complete new drug application process between January 1, 1982 and September 24, 1984 and valproic acid is also the active ingredient in Depakene which was approved before Depakote. It is an axiom of statutory interpretation that the Court should snatch consistency from the jaws of contradiction if Congress' purpose can be discerned. *See Atwell v. Merit Systems Protection Board*, 670 F.2d 272, 286 (D.C. Cir. 1981); *Citizens to Save Spencer County v. E.P.A.*, 600 F.2d 844, 870 (D.C. Cir. 1979). The FDA's equation of "active ingredient" and "active moiety" achieves this end, leaving Depakote with no exclusive marketing privilege beyond September 24, 1986.

Even if Abbott's interpretation of "active ingredient" were accepted by the FDA, the same rules of statutory interpretation would require that subsection (v) be applied to Depakote. The evident purpose of the marketing exclusivity provisions is to reward drug manufacturers for substantial expenditures of time and money for the development of pioneer drugs. In the course of defending the Amendments, Representative Waxman stated:

> We clarified the language [of the Amendments] . . . so that the 3-year provision will apply only when a substantial investment is made in new clinical trials.
>
> . . . .
>
> It would be fine to say that the consumer could get the same drug at a lower price if there were generics of the new drug. But there would not be a new drug to copy if the first company did not put in the money to develop it. What we are saying is if they put the money in to develop it, they ought to

> have a 3-year protection. We have narrowed it to make sure that it is a significant-enough change so that the 3-year rule will apply only when new clinical tests are essential to getting FDA approval and when there is an investment of some magnitude.

Waxman Statement, 130 CONG. REC. at H9124.[10] Describing the Amendments to his colleagues, Representative Waxman also noted:

> [T]he amendment provides a 5-year period of exclusive market life for drugs approved for the first time after enactment of the legislation. This provision will give the drug industry the incentives needed to develop new chemical entities whose therapeutic usefulness is discovered late when little or no patent life remains.

Id., 130 CONG. REC. at H9113.[11] Because Abbott was not required to perform clinical tests for safety and efficacy

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[10] In this statement, the Representative was referring to subsection (ii) of the exclusivity provisions:

> If an application submitted under subsection (b) for a drug, no active ingredient (including ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this subsection [September 24, 1984], no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration five years from the date of the approval of the application under subsection (b) . . . .

21 U.S.C. § 355(j)(4)(D)(ii).

[11] The statutory reference for this statement is subsections (iii) and (iv) of the exclusivity provisions:

> If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of enactment of this subsection [September 24, 1984] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the

in support of its NDA for Depakote, it did not make the investment contemplated by Congress as justification for the longer periods of marketing exclusivity. Consequently, the Court is constrained to resolve the conflict between subsections (i) and (v) in favor of application of the latter, and either definition of "active ingredient" permits only that Depakote's exclusive marketing privilege expired on September 24, 1986.

III. *CONCLUSION*

Although the FDA rejected Abbott's citizen petition in reliance upon expert opinion not disclosed to Abbott, the opinion was based upon scientific data compiled and presented by Abbott and was solicited by the Agency in response to expert opinion submitted by Abbott. Because Abbott was fully aware that classification of Depakote as a salt of Depakene was a critical issue in its petition and Abbott had a complete opportunity to comment on this issue, the Agency's failure to disclose an opinion contrary to Abbott's position does not warrant *de novo* review by

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> approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) for such drug.

21 U.S.C. § 355(j)(4)(D)(iii).

> If a supplement to an application approved under subsection (b) is approved after the date of enactment of this subsection [September 1984] and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

Id. § 355(j)(4)(D)(iv).

the Court or remand to the Agency. Further, the Agency's finding that Depakote is a salt of Depakene was a reasonable resolution of conflicting evidence.

The same cannot be said, however, of the Agency's legal conclusion that the term "active ingredient" must be read as "active moiety" for the purposes of the exclusivity provisions of the Hatch-Waxman Amendments but given a contradictory definition in the ANDA provisions of the Amendments. Though the reasoning of the FDA is plausible, it finds no support in the language of the statute or the legislative history and is inconsistent with the complementary nature of the two portions of the Amendments. In the absence of congressional direction to the contrary, whether express or implied, the term must be given the same meaning throughout section 355(j).

Whichever definition is assigned, the result in this case is unfavorable to Abbott. If "active ingredient" is read as "active moiety," section 355(j)(4)(D)(v) unquestionably applies to Depakote, leaving the drug without exclusive marketing privileges after September 24, 1986. The same result flows from definition of the term as the ingredient in the final dosage form of the drug. While subsection (i), which allows ten years of exclusive marketing, is applicable to Depakote using this definition, subsection (v) is also applicable. The conflict is resolved by reference to the purpose of the Hatch-Waxman Amendments; namely, to preclude for a specified period generic competition against drugs as to which substantial investments had been made in clinical investigations. Because Depakote was approved entirely upon the clinical investigations conducted for Depakene, Congress' purpose is served only by restricting Depakote to two years of exclusive marketing.

/s/ Oliver Gasch
OLIVER GASCH
United States District Judge

Date: July 24th 1988

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 88-0474-OG

ABBOTT LABORATORIES,
Plaintiff,

v.

DR. FRANK E. YOUNG, Commissioner,
Food and Drug Administration,
Defendant.

ORDER

[Filed Jul. 25, 1988]

Upon consideration of the defendant's Motion for Summary Judgment, the plaintiff's Cross-Motion for Summary Judgment, the oppositions thereto, and the record herein and for the reasons stated in the accompanying memorandum, it is by the Court this 24th day of July, 1988

ORDERED that defendant's Motion be, and hereby is, granted; and it is further

ORDERED that plaintiff's Motion be, and hereby is, denied.

/s/ Oliver Gasch
OLIVER GASCH
United States District Judge

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

Feb. 11, 1988

Bryan Jay Yolles, Esq.
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Clifford & Warnke
815 Connecticut Avenue
Washington, D.C. 20006

Re: 86P-0367/CP
86P-0367/PSA

Gentlemen:

This is in response to your petitions to the Food and Drug Administration (FDA) on behalf of Abbott Laboratories (Abbott) seeking 10 years of exclusive marketing under sections 505(c)(3)(D)(i) and 505(j)(4)(D)(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for the product Depakote described in new drug application 18-723 and approved for marketing on March 10, 1983. The citizen petition (86P-0367/CP) and the petition for stay (86P-0367/PSA) were both dated August 29, 1986 and filed by our Dockets Management Branch on September 2, 1986. One supplement to the petition was filed October 9, 1986, and another supplement, containing information in response to an agency request for additional information, was filed February 5, 1987. On February 12, 1987, a meeting was held at Abbott's request in which the firm made a presentation concerning the nature of the active ingredient in Depakote. This was followed up by a letter, dated February 27, 1987, to FDA's General Counsel's office "to clarify certain points" made during the meeting.

In accord with agency policy for petitions concerning marketing exclusivity, we published a notice of your petition in the *Federal Register* that allowed 30 days, later extended at your request by 10 additional days, for interested persons to comment. (51 FR 40520) we received two comments opposing the citizen petition, and one comment opposing the second supplement.*

The citizen petition requests that the agency reconsider its determination that the exclusive marketing period the Food and Drug Administration (FDA) accorded Depakote during which no generic copies of the drug could be approved extended only to September 24, 1986, under sections 505(c)(3)(D)(v) and 505(j)(4)(D)(v) the Act. The petition argues that Depakote should have been accorded 10 years of exclusive marketing under sections 505(c)(3)(D)(i) and 505(j)(4)(D)(i) of the Act.

The petition is accompanied by a request for a stay of approval of abbreviated new drug applications (ANDA's) and section 505(b)(2) applications referred to in the petition as paper NDA's) submitted for generic copies of Depakote pending issuance of a response to the citizen petition and for 30 days thereafter if the citizen petition is denied.

We have carefully reconsidered our decision on the period of exclusivity to which the Depakote product is entitled in light of all of Abbott's arguments and data. We again find that Depakote is entitled to two years of exclusivity, but does not meet the requirements that entitle a product to 10 years of exclusivity. In addition, we find that requirements for a stay have not been met in that sound public policy grounds supporting the stay have not been demonstrated, nor has it been shown that the delay result-

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* All comments state that the petition is incorrect in its arguments that Depakote falls within the requirements for 10-year exclusivity, and that for FDA to grant the petition would set an undesirable precedent. The comments also allude to questions of patent status that are not within FDA's province.

ing from the stay is not outweighed by public health or other public interests. We therefore deny both the petition for ten-year exclusivity and the request for stay.

The 10-year period of exclusive marketing granted by sections 505(c)(3)(D)(i) and (j)(4)(D)(i) is the longest granted by the statute and is intended to reward significant research and development of new molecular entities not previously approved for marketing. The statute confers 10 years of exclusivity on drug products approved in a "window period" between 1982 and September 24, 1984 that contain "no active ingredient (including any ester or salt of the active ingredient)" that has ever been approved in any previous application. The statute also provides five years of exclusivity for such products approved after September 24, 1984 and shorter periods of exclusivity for changes in already approved drugs. (See Attachment A)

When Abbott submitted its application for approval of Depakote in 1981, Abbott took the position that there was no need to conduct any clinical studies to establish the safety or effectiveness of Depakote, because the active ingredient in Depakote was essentially the same as the active ingredient in Abbott's previously approved Depakene,* and both products were intended for the same uses, i.e., in the treatment of epileptic seizures. FDA agreed with Abbott, concluding that the only significant difference between the two products was that Depakote was an enteric coated tablet that reduced gastro-intestinal irritation, while Depakene was a soft gelatin capsule or syrup. Now Abbott argues that Depakote is an entirely new chemical entity, not at all like Depakene, and that despite the absence of significant research or develop-

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* The new drug application (NDA 18-081) for Depakene itself had been approved prior to the January 1, 1982 date with which the "window" period for exclusivity commences. Thus there is no basis to claim exclusivity for the product that is the subject of that application.

ment associated with Depakote, Abbott should be rewarded with ten years of exclusive marketing.

FDA has carefully examined the chemical structures of the active ingredients in Depakote and Depakene and has concluded that the active ingredient in Depakote is simply a salt of valporic acid, the active ingredient in Depakene. Depakote thus does not qualify for ten years of exclusivity under the plain language of sections 505(c)(3)(D)(i) and (j)(4)(D)(i) of the Act. Moreover, FDA does not believe that Congress intended the 5 and 10 year exclusivity provisions to reward manufacturers for making minor changes in already approved products. A more detailed explanation of FDA's decision follows:

I. *ABBOTT IS ENTITLED TO TWO YEARS OF EXCLUSIVITY FOR DEPAKOTE BUT NOT TO ANY LONGER PERIOD.*

The Drug Price Competition and Patent Term Restoration Act (the 1984 Amendments) created five steps of exclusivity, which confer upon certain qualifying drugs two to ten years of exclusive marketing, depending upon the innovation the drugs represent and the probable cost of their research and development. The exclusivity provisions are summarized immediately below and in attachment A. (The legislative background of the provisions is described in part II, B).

The two-year exclusivity provision, found in sections 505(j)(4)(D)(v) and 505(c)(3)(D)(v), prohibits the agency from making approval of an ANDA or an application described in section 505(b)(2) for a generic product effective until September 24, 1986 for a "drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application . . . during the period beginning January 1, 1982 and ending on the date of enactment of this subsection [September 24, 1984]." This provision is ap-

plicable to Depakote because its active ingredient is a salt of valproic acid, a previously approved ingredient, and it was approved on March 10, 1983.

There are two types of three-year exclusivity. They are found in sections 505(j)(4)(D)(iii) and (iv) and 505(c)(3)(D)(iii) and (iv). The first type prohibits the agency from making immediately effective an approval of an ANDA or an application described in section 505(b)(2) for a generic version of "a drug which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application . . ., [if the drug is the subject of an application approved after September 24, 1984,] and . . . if the application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." Sections 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii).

The second type of three-year exclusivity prohibits the agency from making immediately effective approval of a generic drug for a change (e.g., a new indication) approved after September 24, 1984 in a supplement that contains reports of new clinical investigations essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement. Sections 505(c)(3)(D)(iv) and 505(j)(4)(D)(iv). Neither of the three-year exclusivity provisions is applicable to Depakote, because the drug was neither approved after September 24, 1984, nor the subject of new clinical investigations conducted or sponsored by Abbott.

The five-year exclusivity provisions, found in sections 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii), prohibits the submission of an ANDA or application described in section 505(b)(2) for a drug first approved after September 24, 1984, no active ingredient including any salt or ester of the active ingredient of which had previously

been approved. The 10-year exclusivity provision, found in sections 505(j)(4)(D)(i) and 505(c)(3)(D)(i), delays for 10 years the effective date of the approval of an ANDA or application described in section 505(b)(2) for a drug first approved during the "window period" (January 1, 1982-September 24, 1984), no active ingredient (including any salt or ester of the ingredient) of which has been approved in any other application.

Neither the five nor the ten-year exclusivity provision applies to Depakote because it is not a never-before approved active ingredient under the terms of the provision, but rather, is a salt of the previously approved ingredient, valproic acid.* Because this is a key area of dispute between Abbott and FDA, we elaborate on the basis for this conclusion below.

II. *THERE IS NO LEGAL OR SCIENTIFIC BASIS FOR ACCORDING DEPAKOTE TEN YEARS OF EXCLUSIVITY AS A DRUG "NO ACTIVE INGREDIENT (INCLUDING ANY ESTER OR SALT OF THE ACTIVE INGREDIENT) OF WHICH HAS BEEN APPROVED."*

A. *Depakote Contains a Salt of a Previously Approved Active Ingredient, Valproic Acid.*

The active ingredient in Depakote falls within the definition of a salt. The following is a standard chemical definition of a salt:

> "*Salt* (1) The compound formed when the hydrogen of an acid is replaced by a metal or its equivalent (e.g., an NH_4 radical). Example:
>
> $$HCL + NaOH \rightleftarrows NaCL + H_2O$$

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* In addition, the five-year provision is inapplicable because it applies to drugs approved after passage of the 1984 Amendments, whereas Depakote's approval took place during the "window" period prior to enactment.

This is typical of the general rule that the reaction of an acid and a base yields a salt and water. See also soap. Most inorganic acids ionize in water solution.

(2) Common salt, sodium chloride . . . ."

soap . . . "A soap is actually a specific type of salt (q.v.), the hydrogen of the fatty acid being replaced by a metal, . . . usually sodium." *

The process described by the definition describes exactly what happens in the formulation of Depakote from valproic acid. In Depakote's synthesis, which begins with valproic acid, the hydrogen of the valproic acid is replaced by sodium, a metal. This yields the salt of valproic acid and water. Moreover, the synthesis of Depakote is analogous to the textbook's example of a soap, in that valproic acid [2-n-propylpentanoic acid, C_{18} H_{15} O_2, or $(C_3$ $H_7)_2$ CH-COOH] is a homologue of the recognized and usual organic acids (such as myristic acid, C_{12} H_{23} O_2, or stearic acid, C_{18} H_{35} O_2) observed in soaps.

The active ingredient in Depakote is also appropriately classified as a salt of valproic acid under the official rules of nomenclature for chemical compounds, the International Union of Pure and Applied Chemistry (IUPAC) Rules for Nomenclature. *See* affidavit of Robert H. Wood, Ph.D. (Attachment B). Under those rules, the active

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* *The Condensed Chemical Dictionary*, 10th Ed. (rev. by G.G. Hawley), vanNostrand Reinhold, New York, 1981. See also: *"Salt* . . . 1 . . . d: any of numerous compounds that result from replacement of part or all of the acid hydrogen of an acid by a metal or a radical acting like a metal: an ionic or electrovalent crystalline compound . . ." *Webster's New Collegiate Dictionary*, G. & C. Merriam Co., Springfield, Massachusetts, 1979. And see: *"Salt* . . . 1 sodium chloride or common salt 2. any compound of a base and an acid; any compound of an acid some of whose replaceable hydrogen atoms have been substituted . . ." *Dorland's Illustrated Medical Dictionary*, 25th Ed., W. B. Saunders, Philadelphia, 1974.

ingredient in Depakote is appropriately named sodium hydrogen divalproate (or sodium hydrogen (bis)valproate) and is thereby classified as an acid salt of valproic acid, under §§ 6.1 and 6.3. *Id.* at paragraphs 5-7. This is the name that Chemical Abstract Service (CAS) has given the compound. CAS is an objective source of chemical names, and the name it has given the active ingredient in Depakote shows that CAS, like FDA, has concluded that the compound is a salt of valproic acid.

Abbott's Arguments

Except for a brief reference in a July 10, 1986 letter attached as an exhibit to its petition, Abbott has never provided a formal definition of a salt, or disputed either FDA's definition or the fact that Depakote's formulation is consistent with standard definitions. Rather, Abbott has relied in its arguments upon descriptions of typical salts, and compared Depakote's physical properties to the properties of such salts in an attempt to differentiate Depakote from them. These examples do not prove that Depakote fails to meet the definition of a salt; they merely illustrate that Depakote, like a number of other salts, does not have all properties of the most typical salts.

Abbott first argues in its July 10, 1986 letter to FDA that Depakote is not a salt of valproic acid, on the following grounds: "[D]ivalproex sodium is an oligomeric complex and not a salt of valproic acid. If a salt at all, it is an acid salt. If an acid salt, at best it is an acid salt of divalproic acid."

Abbott's characterization of the compound does not remove it from classification as a salt. The term "salt" is used without qualification in the exclusion from exclusivity found in section 505(c)(3)(D)(i) and (ii) and 505(j)(4)(D)(i) and (ii) of the Act. FDA believes, therefore, that Congress intended a broad definition of "salt" and did not intend to permit applicants to gain

5 or 10 years of exclusivity by artificially narrowing common scientific definitions of terms used in the Act.

Abbott argues that Depakote is not a salt of valproic acid because there is some valproic acid remaining in the final product. However, the presence of the remaining valproic acid does not remove Depakote from the definition of a salt. As Abbott concedes, the remaining acid in Depakote merely characterizes it is an "acid salt" rather than as a "normal salt." Under the IUPAC Rules for Nomenclature, an acid salt is simply a subcategory of salt. Because the statutory exclusion from the 10-year exclusivity provision for salts of previously approved products does not distinguish between types of salt, FDA concludes that an "acid salt" of a previously approved compound is not entitled to exclusivity.

Abbott also places great reliance on certain evidence suggesting that sodium hydrogen divalproate may be an "oligomeric complex." However, characterizing Depakote as an "oligomeric complex" also does not remove it from the definition of a salt. Assuming *arguendo* that sodium hydrogen divalproate is an oligomeric complex, FDA is unaware of any reason, and Abbott has offered none, to believe that a salt cannot be an oligomeric complex. As Dr. Wood's affidavit states, the type of hydrogen-bonding or coordination-bonding postulated by Abbott as the basis for Depakote's possible oligomeric structure does not change the appropriate classification of the compound as a salt. Only if the synthesis of sodium hydrogen divalproate produced new covalent bonds (rather than hydrogen or coordination bonds) would the compound's classification as a salt of valproic acid be invalidated. *See* affidavit of Dr. Wood at paragraphs 12 and 13. Abbott has not claimed any change in covalent bonding, nor does the evidence concerning the structure of the compound support such a claim.

Finally, Abbott's claim that Depakote is a salt of "divalproic acid," does not advance the company's argument.

Abbott has not demonstrated the existence of, nor are we aware of, any chemical entity properly characterized as "divalproic acid." Abbott's claim that Depakote is a salt of "divalproic acid" may derive from the official name of the compound, "sodium hydrogen divalproate," or the USAN term "divalproex sodium." However, as Dr. Wood's affidavit establishes, the term "*di*valproate" or "*di*valproex" simply indicates that there are two valproate anions to one sodium anion in the compound; it does not indicate the existence of an entity called "divalproic acid." *See* affidavit of Dr. Wood at paragraph 7. The use of the prefix "di" is simply a method of counting the valproate units, regardless of whether those valproate units are bound together in a compound that would appropriately be called "divalproic acid." Moreover, the evidence offered by Abbott about the structure of the compound does not support the conclusion that the valproate anions in sodium hydrogen divalproate are joined by covalent bonds, nor is there any other reason to believe that a chemical called "divalproic acid" exists. Thus, there is no scientific basis for Abbott's claim that sodium hydrogen divalproate is a salt of "divalproic acid."

As Dr. Wood's affidavit states, the IUPAC rules on salts cite the compound "hexasodium chloride fluoride bissulphate." The term "*bis*sulphate" (like *di*valproate) shows that "the compound is a salt containing two sulphates, *not* that it is a salt of bissulphuric acid; "bissulphuric acid" is unknown just as "divalproic acid" is unknown." Wood affidavit at paragraph 6.

Indeed, Abbott itself has elsewhere recognized that the number of valproate anions in related compounds is irrelevant to the nature of these compounds as salts of valproic acid. For example, in U.S. Patent No. 4,598,070, Abbott refers to a compound containing a metal, three hydrogens, and four valproate anions ("potassium trihydrogen tetravalproic acid") as an "acid salt of valproic acid." Consistency with its position in this case

would have required Abbott to call the compound in U.S. Patent No. 4,598,070 a salt of "tetravalproic acid." Instead, outside of this bid for exclusivity, Abbott recognizes the standard scientific nomenclature.

Abbott's October 9, 1986 supplement encloses a one-paragraph handwritten note by an FDA employee that Abbott obtained under a Freedom of Information Act request in which Depakote is referred to as "the sodium salt of divalproic acid." Abbott attempts to argue that the note establishes that FDA recognizes the independent existence of divalproic acid. This is incorrect. As is apparent from the full text of the note, its purpose was to explain that Depakote is not a new chemical entity and that it did not require new clinical studies because it is essentially the same as Depakene. The reference to "divalproic acid" was probably a quotation from an explanation supplied to FDA by the sponsor, and not a matter of concern for FDA at the time. Whether to consider Depakote a salt of valproic acid or of the theoretical concept of "divalproic acid" had little regulatory significance when the application was submitted, because the exclusivity provisions had not been enacted. Abbott leaps to the conclusion that the memo "is consistent with Abbott's claim that Depakote (divalproex sodium) is a distinct new ingredient . . ." but this is contrary to the very point of the note, which was to explain that the product is not new. The fact that the note refers thereafter to the Depakene new drug applications for information on Depakote's pharmacological and toxicological properties is entirely in accord with FDA's consistent position that Depakote is not a new chemical entity.*

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* In any event, under FDA regulations a written statement of an agency employee, unless offered under 21 CFR 10.85 or 10.90, represents the best judgment of that employee at that time but does not necessarily represent the formal position of FDA, and does not bind the agency to the views expressed. 21 CFR 10.85(k).

Thus, FDA concludes that Depakote contains a salt of valproic acid. Even if there were a basis for also considering the ingredient in Depakote to be a salt of divalproic acid, it would still be properly considered a salt of valproic acid. However, the name "sodium hydrogen divalproate" does not suggest the existence of an entity called "divalproic acid," nor has such an entity been shown to exist. Finally, the available information, e.g. in *Chemical Abstracts*, on the synthesis of Depakote does not indicate that an entity such as "divalproic acid" is used in its manufacture.

Abbott places great reliance on its argument that some of Depakote's physical properties are inconsistent with its being a salt. However, Abbott's evidence demonstrates only that the compound is not a typical salt.

Abbott argues that sodium hydrogen divalproate cannot be a salt because of its high molecular weight when dissolved in tetrahydrofuran. As Dr. Wood observes in his affidavit, the compound's molecular weight in solution is irrelevant to its classification because hydrogen-bonded species like sodium hydrogen divalproate can dissolve as monomers (with low molecular weight) or as oligomers (with high molecular weight), depending on the solvent used. Wood affidavit at paragraph 10.

Abbott also argues that the results of its Fast Atom Bombardment Mass Spectrometry study show that sodium hydrogen divalporate cannot be a salt. This evidence merely shows that the compound has strong hydrogen and coordination bonds in the solid state. As discussed earlier, hydrogen and coordination bonding do not affect the classification of a compound as a salt. Only covalent bonding, which the evidence does not reveal, could change the classification.

The solubility of sodium hydrogen divalproate in nonpolar solvents also does not remove it from classification as a salt. Although typical salts are not soluble in nonpolar solvents, other salts, like the tetraalkylammonium

nitrates and picrates, are. See Wood affidavit at paragraph 13.

Finally, Abbott's reliance on the low melting point of sodium hydrogen divalproate is misplaced. Although many salts have higher melting points, others, like ethylammonium, melt below 25°C. See Wood affidavit at paragraph 14.

Thus, there is no scientific basis for Abbott's claim that only compounds with the properties of typical salts can be considered salts, or that sodium hydrogen divalproate is not a salt because it does not share all the properties of typical salts. Abbott's reference to the definition of a salt in the chemistry textbook by Masterton and Slovensky, that a salt is an ionic compound, similarly oversimplifies the nature of salts. Few, if any, salts are purely ionic in structure.

Abbott also argues that Depakote should be considered a never-before-approved active ingredient under the terms of the statute because the structure and chemical and physical properties of Depakote are "dramatically diffferent" from those of sodium valporate and valproic acid. The information Abbott submitted does not, however, establish that Depakote contains a never-before-approved active ingredient for purposes of the exclusivity provisions of the Act. The listing of physico-chemical properties submitted by Abbott show that Depakote is indeed distinguishable from valproic acid and sodium valproate. However, Depakote contains no chemical bonds (i.e., covalent bonds) not found in valproic acid and sodium valproate; it is a salt of valproic acid, a known chemical entity, albeit an atypical salt. The properties of Depakote are in accord with the known collegiative properties and tendencies of organic acids and their salts.

Abbott also argues that the nomenclature describing Depakote ("divalproex sodium") in *USAN And The USP Dictionary of Drug Names* indicates that Depakote is a never-before-approved active ingredient. The petition states that divalproex sodium, valproic acid and sodium

valproate are separately listed in this dictionary, and that the publication is "formally recognized by the FDA as authoritative in connection with the identification of 'new chemical entities.'" Abbott misunderstands the use FDA and others make of USAN. The listings in USAN facilitate communication regarding chemicals that, to be described more completely and accurately, might require a number of polysyllabic words. The shorthand USAN listings, therefore, provide "common" names that are relatively easy to use, and adequate for ordinary communication. However, FDA would not, and has nowhere stated that it would, recognize every drug listed in USAN as a new chemical entity for purposes of the exclusivity provisions. The introductory portions of USAN included with the petition state that the purpose of the dictionary is to establish and facilitate "*common*" nomenclature, but the data for its listings "usually originates from a firm or an individual who has developed a substance." (Emphasis added.) Further, the dictionary itself warns that "it should be emphasized that while the Council can ascertain the preferred chemical nomenclature for a structure claimed for any compound of definite compositions, the Council is not in a position to confirm the structure or the claims for pharmacologic activity." (Preface, Page 8).

We thus regard the "divalproex sodium" nomenclature for Depakote in USAN (and in FDA's computerized record of approved NDA's) as a useful identification differentiating the product from others, but one that is not intended to nor should be considered definitive in establishing the structure and properties of Depakote, or determining whether the drug is a new chemical entity for purposes of exclusivity. The USAN name "divalproex sodium" is simply a convenient shorthand; an official and more technically complete name is provided under the International Union of Pure and Applied Chemistry (IUPAC) Rules for Nomenclature. As explained in Dr. Wood's affidavit (nos. 6 and 7) under those rules, the active ingredient in Depakote is appropriately named sodium hydrogen

divalproate [or sodium hydrogen (bis) valproate] and is thereby classified as an acid salt of valproic acid. As described above, the use of the prefix "di" is simply a method of counting the number of valproate units in the compound, regardless of whether or how those valproate units are bound together. The names "sodium hydrogen divalproate" and "divalproex sodium" thus show that the compound is an acid salt of valproic acid. They do not establish that the compound is a salt of "divalproic acid."

Abbott also maintains that FDA must have believed that an entirely new and different ingredient is formed when valproic acid and sodium hydroxide are combined, because otherwise FDA would or should have required that the firm perform clinical studies to show that Depakote complies with FDA's combination policy, 21 CFR 300.50.* However, FDA accepted the view of Abbott that it was neither a combination nor a new chemical entity. The view advanced by the company and accepted by FDA at the time the product was under review was that Depakote is merely a fortuitous manipulation by which an entity previously marketed as a liquid or soft gelatin capsule and called Depakene can be formulated into an enteric-coated tablet form. The active moiety in both Depakote and Depakene, that is the substance by which the drugs achieve their therapeutic effects in the body, is valproic acid in both cases.

Furthermore, as Abbott is well aware, if FDA had believed that an entirely new and different ingredient were created in the synthesis of Depakote, consistent FDA

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* Abbott quotes an August 12, 1986 FDA letter explaining that the agency had not classified Depakote as a new chemical entity because it had determined that the product was not a new chemical entity but rather a compound composed of the previously approved active ingredient (valproic acid) and its previously approved salt (valproate sodium). Upon re-examination, we believe that it is correct to describe Depakote merely as a salt of Depakene (valproic acid.)

policy in all the Divisions of the Office of Drug Research and Review would be to require clinical studies in support of the safety and effectiveness of that ingredient. Such studies were not required, of course, because there was no evidence to show that Depakote is anything other than a enteric-coated version of the already approved Depakene.

B. *The Legislative Policies Underlying the Exclusivity Provisions Are Not Served by Granting 10-Years of Exclusivity to Depakote.*

Even if there were some limited sphere in which Abbott's extremely narrow view of the definition of a salt, and its correspondingly broad definition of "new molecular entity," were appropriate, those definitions are plainly inconsistent with Congress' purposes in adopting the 1984 Amendments in general and the exclusivity provisions in particular.

The 1984 Amendments amended the Act in two important respects. Title I of the 1984 Amendments authorizes FDA to accept abbreviated new drug applications (ANDA's) for generic copies of already approved drugs. Prior to the 1984 Amendments, abbreviated applications were permitted only for generic versions of drugs first approved before 1962. In extending the ANDA procedure to post-1962 drugs, Congress stated that it intended to make available more low cost generic drugs. *See, e.g.*, H.R. 98-857, Part 1, 89th Cong., 2d Sess. 14 (1984).

Title II, the Patent Term Restoration portion of the 1984 Amendments, was intended to create a new incentive for expenditures for research and development of certain products which, because they are subject to premarket approval, may lose the benefit of some of the years of exclusive marketing protection provided by their patents. Under this title, a product may under certain circumstances be entitled to an extension of up to five years on its period of patent protection. Thus, the exclusivity

provisions at issue in the petition are not the only mechanism, and not even the primary mechanism, by which Congress made sure that adequate benefits would continue to accrue for research and development of innovative drug products.

According to a key House member involved in drafting the 1984 Amendments, the exclusivity provisions were intended "to assure drug companies were rewarded for *major new innovations* involving either a new drug or a new use of an already marketed drug. While patents usually cover such new innovations, Congress wanted to guarantee a limited period of exclusive marketing." November 19, 1985 letter submitted by Congressman Henry A. Waxman, Chairman, Subcommittee on Health and Environment, to FDA Doc. No. 85P-0409. (Emphasis added.)*

The table provided as attachment A shows all of the exclusivity provisions in § 505(j)(4)(D) of the Act. The exclusivity provisions at § 505(c)(3)(D) are analogous.

As illustrated in the table, the statute provides proportionately greater periods of exclusivity in circumstances where proportionately greater expenditures for development of safety and effectiveness data and more significant therapeutic benefits would be typical. Thus, for example, under the statute's general exclusivity provisions,

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* While a pioneer drug's period of exclusive marketing protects it against competition from generics approved on the basis of ANDA's or section 505(b)(2) applications, it does not assure its manufacturer a monopoly. Competitors theoretically could still secure approval by performing pre-clinical and clinical studies to satisfy the requirements for an NDA; because of the expense involved, however, it is highly unlikely that this would be done. In this instance, granting 10 years of exclusivity to Depakote would have the effect of requiring a would-be competitor to conduct full-scale preclinical and clinical trials on sodium hydrogen divalproate, a task never required of Abbott because of the compound's similarity to the already tested valproic acid.

three years of exclusivity would be accorded a drug that includes a previously approved active ingredient (including a salt or ester of the active ingredient) and whose application contains reports of new clinical investigations conducted or sponsored by the applicant and essential to the approval. Five years of exclusivity would be accorded a drug no active ingredient (including a salt or ester of the active ingredient) of which has previously been approved, because typically, a never-before approved active ingredient would provide significant therapeutic benefits and would require substantial investment not only in new clinical studies, but also in basic pre-clinical and pharmacological data.

As explained previously, the statute's "transition" provisions provide exclusivity for approvals that took place during the "window" period just prior to enactment of the statute. Thus, for example, the five-year period for drugs containing a never-before-approved active ingredient becomes a ten-year period for a product approved during the "window."

FDA does not believe that Congress intended to provide five or ten years of exclusivity for minor changes in already approved drugs that involve less research and innovation than that required to qualify for three years of exclusivity. In the floor debates on the 1984 Amendments, Congressman Waxman explained that the three-year exclusivity period was intended to reward significant investment and innovation and was therefore to be available to a drug company

> that puts in the money as an investment to develop a product that will have to be approved by FDA and requires clinical tests, *which means it is not just some minor change in a chemical entity that has previously been approved, but a change that is significant enough to require clinical tests.*

Cong. Rec. H9124 daily ed. Sept. 6, 1984 (emphasis added).

Abbott's Depakote met the safety and effectiveness requirements for marketing not by developing new data, but by relying on the safety and effectiveness data in Abbott's previously approved new drug application for valproic acid (Depakene). Abbott's new drug application (NDA 18-723) providing for Depakote enteric coated tablets in two different strengths was approved by FDA on March 10, 1983. In its application, and in its current petition, Abbott makes no claim that its application relied for its approval upon new clinical studies performed on Depakote. Rather, Abbott cross-referenced the data from pre-clinical and clinical studies in its new drug application for Depakene (valproic acid) as evidence of the safety and effectiveness of Depakote. FDA approved Depakote on this basis because it concluded that there were no significant chemical or pharmacological differences between Depakote and Depakene other than Depakote's enteric coating. Thus, the drug would not have been eligible for three years of exclusivity because no clinical trials were required for approval.

In this petition, Abbott seeks to have the agency interpret the five and ten year exclusivity provisions so as to confer ten years of exclusivity on a drug so similar to an already approved drug that Congress would not have given it even three years of exclusivity. FDA does not believe that this is a reasonable interpretation of the five and ten year exclusivity provisions, nor that Congress intended the agency to interpret the five or ten year exclusivity provisions in such a way as to apply to drugs like Depakote, which are minor variations on already approved drugs and represent neither substantial investments in research and development nor significant therapeutic innovations.

C. *The FDA is Not Required to Apply ANDA-Eligibility Principles to Exclusivity Determinations.*

The petition seeks to rely on two letters (one to Pharmacaps, Inc., and one to Rowell Laboratories, Inc.) that FDA has written in response to petitions requesting permission under section 505(j)(2)(C) of the Act (the ANDA eligibility provisions) to submit abbreviated new drug applications (ANDA's) for variations of approved drug products. In each of the two letters cited by Abbott, FDA denied permission to submit an ANDA for a proposed product on the ground that the product did not contain the "same active ingredient" as any already approved product, as required under section 505(j)(2)(A)(ii) for single-ingredient products. In reaching this determination, the agency concluded that to be considered the "same active ingredient" for purposes of ANDA eligibility, the active ingredient in the proposed product must be the same in its final dosage form as the active ingredient in the approved product, regardless of whether the two products produced the same active moiety after administration (e.g., circulating in the blood).

Abbott now argues that the phrase "no active ingredient (including any ester or salt)" in the exclusivity provisions of the Act must necessarily be given the same interpretation as the phrase "same active ingredient" in section 505(j)(2)(A)(ii). Abbott thus contends that if there is any difference between a new and previously approved product in their final dosage forms, FDA is required to consider the new product a "new chemical entity," unless the new product is a salt or ester of the approved product. Relying on its view that Depakote is not a salt of Depakene, Abbott thus argues that FDA must consider Depakote a "new chemical entity" because it differs from Depakene in its final dosage form.

If FDA adpoted Abbott's interpretation, any minor manipulation (other than a salt or ester) of a previously

approved drug would be entitled to the maximum period of exclusivity, even if it did not represent any change in the basic activity moiety. FDA does not believe that Abbott's interpretation is consistent with Congressional intent, nor is it mandated by FDA's interpretation of "same active ingredient" for purposes of permitting the marketing of new drug products through abbreviated applications. This interpretation of "same active ingredient" is inapplicable to the agency's determination of the period of exclusivity for which Depakote qualifies, on two independent grounds. First, as already explained, Depakote is a salt of an already approved active ingredient and thus does not fall within the plain language of eligibility for the exclusivity provisions at issue. Second, neither the language of, nor the policies underlying, the exclusivity provisions are the same as those of the ANDA eligibility provisions in section 505(j)(2)(C).

The petitions submitted by Pharmacaps and Rowell Laboratories under section 505(j)(2)(C) each requested permission to submit an ANDA for a single-ingredient product in which the active ingredient was to be significantly changed from that of an already approved product.[1] For single-ingredient drug products, an ANDA may be submitted only for a drug that has the "same active ingredient." Section 505(j)(2)(A)(ii)(I). The purpose of this requirement for single-ingredient products is to prevent the submission of ANDA's, which contain no safety and effectiveness information, for products whose single active ingredient has never been shown to be safe and effective.

In responding to these petitions and deciding whether an ANDA could be submitted for the proposed products, FDA was required to interpret the term "same active ingredient." The agency concluded that Congress intended the traditionally narrow interpretation of "active

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[1] In each case, the substitute ingredient represented not only a difference in final dosage form, but a difference in active moiety.

ingredient" in sections 505(j)(2)(A)(ii)(I) and (j)(2)(C), because the term does not have the qualifying parenthetical phrase "(including any ester or salt of the active ingredient)" that it has in the exclusivity provisions. In addition, a narrow interpretation is necessary to effectuate the public health purposes of that section and of the Act, because safety and effectiveness questions may be raised by a difference between two drug products either in their final dosage form or in their active moiety.

In contrast to the unqualified use of the term "active ingredient" in section 505(j)(2)(C), the exclusivity provision relied on by Abbott confers 10 years of exclusive marketing on "a drug, no active ingredient (including any ester or salt of the active ingredient of which has been approved in any other application" and which was approved between January 1, 1982, and September 24, 1984. The explicit inclusion of salts and esters in the statute's parenthetical explanation of "prior-approved active ingredient" makes clear that Congress did not intend a narrow definition of "active ingredient" in the exclusivity provisions, but instead intended to refer to the active "moiety" in a drug (i.e., that part of the chemical compound that defines its pharmacological behavior), rather than to its superficial chemical structure, e.g., the particular ester or salt of the active moiety that happens to be marketed.

FDA's interpretation of the five- and ten-year exclusivity provisions is consistent not only with the statutory language but with the legislative history, which shows that Congress did not intend to grant even three years of exclusivity for making minor changes in an already approved active moiety. Cong. Rec. H9124 (daily ed. Sept. 6, 1984). This interpretation of "new chemical entity" is also consistent with FDA's longstanding definition of the term "new molecular entity" in the agency's IND/NDA classification scheme, which was in effect at

the time the 1984 Amendments were under consideration in Congress.[2]

Finally, FDA's interpretation is consistent with the purpose of the exclusivity provisions, which is to reward major innovations requiring substantial investment in research and development. FDA does not believe that it would be consistent with this purpose to interpret the exclusivity provisions for new chemical entities in such a way as to reward manufacturers for making minor changes in the chemical structure of a final dosage form of an already approved drug, if the changes do not represent any change in the active moiety, and would not even qualify for three years of exclusivity.[3]

D. *Depakote Is Not A New Chemical Entity, Even Though Valproic Acid Was Approved Before Its Salt.*

Finally, Abbott implicitly argues that even if Depakote *is* a salt of valproic acid, it is still entitled to 10 years of exclusivity. Abbott's February 27 letter states that the language of the statute "is unambiguous," and restates the ten-year provision as follows: "a drug is entitled to ten years' market exclusivity if that drug was approved between January 1, 1982, and September 24, 1984, and *neither* the active ingredient of the drug, *nor* a salt or ester of that active ingredient, was previously approved" (emphasis added). Thus, under Abbott's re-

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[2] The term "new molecular entity" is defined in the IND/NDA classification system, as follows:

a. *Chemical Types*

Type 1—New molecular entity—i.e., the active moiety is not yet marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product.

[3] FDA notes that the active moiety in Depakote is valproic acid (or the valproate ion). Thus, under FDA's interpretation of the scope of the ten-year exclusivity provision, Depakote would not be entitled to ten years of exclusivity even if it were not technically a salt of valproic acid.

statement, whenever the first product containing a given active moiety is in a salt or ester form subsequent compounds containing the active moiety are not entitled to exclusivity. When, however, the first product containing the active moiety is not in a salt or ester form, subsequent salts and esters would be entitled to exclusivity as if they were new chemical entities. In the present case, Depakote, while a salt of the previously approved valproic acid, would be entitled to exclusivity because valproic acid, the first marketed version of the moiety, is not a salt or ester of Depakote.

As is apparent by comparison with the actual language shown above of the 10-year exclusivity provision, Abbott's restatement of the statutory language is inaccurate. Abbott has taken the statutory phrase "no active ingredient (*including* any ester or salt . . .)" and changed it to "neither . . . nor . . ." This would be correct only if the original phrase in the statute had been written "*no* . . . (*or* any ester or salt . . .)" FDA interprets Congress' use of the phrase "*including* any ester or salt" rather than "*or* any ester or salt" to mean that esters and salts are intended not as an exhaustive list but as examples of the types of minor variations in chemical structure that Congress did not intend to reward with exclusivity. Thus, FDA belives that Congress intended the phrase "no active ingredient (including any ester or salt)" to refer to the active moiety.

Abbott's restatement of the 10-year exclusivity provision is not only inconsistent with the language of the provision itself, but with the counterpart two- and three-year exclusivity provisions. Those provisions grant two or three years of exclusivity to a drug "which includes an active ingredient (including any ester or salt of the active ingredient)" that has been previously approved and satisfies certain additional requirements. A drug is thus covered under the plain language of the two- and three-year provisions, if, like Depakote, it contains the salt of a

previously approved active ingredient and meets certain other requirements. Yet, according to Abbott's interpretation of the language of the five and ten year provisions, the same drug (i.e., a drug that contains a salt of a previously approved active ingredient) is also entitled to five or ten years exclusivity, but without meeting any additional requirements. This is an absurd result.

The language quoted from the two- and three-year provisions makes clear that these provisions are intended to complement the five- and ten-year exclusivity provisions by providing exclusivity under certain circumstances to those drugs that, because they contain a previously approved active ingredient (including any ester or salt of that active ingredient), are expressly excluded from the five- and ten-year provisions. The only sensible interpretation of these provisions in conjunction with the five and ten year exclusivity provisions is that a compound is *not* entitled to five or ten years of exclusivity if it contains a previously approved active moiety, e.g., where either the new *or* the previously approved drug is simply a different salt or ester. Such a compound may, however, be entitled to three years of exclusivity, if it meets the requirements imposed by the three-year provisions.

Even if the statute could be read as Abbott suggests, the agency would not be required to adopt Abbott's interpretation, because it would lead to absurd results and would be at odds with the plain purposes of the exclusivity provisions. *See, e.g., Bob Jones University v. United States*, 461 U.S. 574, 586 (1983); *United States v. American Trucking Ass'ns*, 310 U.S. 534, 543-44 (1940). Under Abbott's theory, had Depakene been approved after the 1984 Amendments, *both* Depakene (valproic acid) and Depakote would have been entitled to exclusivity as new chemical entities had they been approved in that order. If, under this theory, the order of approval of the two related compounds had been reversed, i.e., if the salt

(Depakote) had been approved before valproic acid (Depakene), valproic acid would *not* be entitled to exclusivity because its salt would have been previously approved. Abbott's interpretation would thus force the agency to grant or deny exclusivity to a base compound or a salt or ester of that base, not on the basis of the types of chemical differences between them or on the degree of innovation, but instead merely on the basis of order of approval.

FDA believes that Congress cannot have intended that the order of approval would dictate eligibility for exclusivity, because such a result would reward (indeed, would provide the maximum period of exclusivity for) marketing strategy rather than significant innovation. The legislative history makes clear that Congress intended exclusivity to reward major innovations and that the periods of exclusivity were intended to be commensurate with the significance of the innovation. Consistent with this purpose, FDA believes that the phrase "active ingredient (*including* any ester or salt)" shows that Congress intended FDA to look beyond superficial chemical differences and to focus instead on significant innovation, i.e., whether the compound contains a new active moiety. FDA's interpretation of the phrase "active ingredient (including any ester or salt)," thus produces a more reasonable result than Abbott's interpretation. Only a major innovation (a new active moiety) is guaranteed ten years of exclusivity under this interpretation. It is immaterial in which order closely related compounds are approved; rather, the determinative issue is the "newness" of the compound for which exclusivity is sought.

FDA concludes that its interpretation of the ten-year exclusivity provision is more consistent with the language and purpose of that provision than Abbott's untenable restatement of that provision. Accordingly, a salt of a previously approved active ingredient is not entitled to ten years of exclusivity.

III. *ADEQUATE GROUNDS HAVE NOT BEEN DEMONSTRATED TO SUPPORT THE REQUESTED STAY OF APPROVAL OF GENERIC DEPAKOTE PRODUCTS.*

The request for stay asks that no abbreviated new drug applications or section 505(b)(2) applications submitted for generic copies of Depakote be approved pending issuance of a response to the citizen petition, and for 30 days thereafter if the citizen petition is denied. No generic copies of Depakote have been approved to date, and therefore the only part of the request that is now relevant is the request for a stay of such approvals for 30 days after issuance of this denial to the citizen petition. The request for the 30-day stay is denied.

FDA's regulations state that the filing of a petition will not stay or otherwise delay any administrative action by the Commissioner unless one of the following applies: (1) the Commissioner determines that a stay or delay is in the public interest and stays the action; (2) a statute requires that the matter be stayed; or (3) a court orders that the matter be stayed. (21 CFR 10.35(d)). The petition argues that the requested stay is in the public interest. Because as we explained in parts I and II above, we have determined that Depakote is entitled only to the expired two-year period of exclusivity originally accorded the product, and not the ten years requested in your petition, applications for the drug submitted under section 505(b)(2) or 505(j) that otherwise meet the requirements for approval are entitled to an approval with an immediate effective date. FDA may not enter into any agreements not to approve products meeting the legal requirements for approval without the permission of any applicants for such products. FDA does not believe that it would be in the public interest, therefore, to grant a stay of the approval of generic copies of Depakote.

FDA's regulations (21 CFR 10.35(e)) also require the Commissioner to grant a stay of action if all the following conditions are met: (1) the petitioner will otherwise suffer irreparable injury, (2) the petitioner's case is not frivolous and is being pursued in good faith, (3) the petitioner has demonstrated sound public policy grounds supporting the stay, and (4) the delay resulting from the stay is not outweighed by public health or other interests. The petition argues that all of the four conditions under which a stay is required exist. We disagree, as follows.

The petition argues that without the stay, Abbott will suffer irreparable injury. Even assuming arguendo that the economic injury cited in the petition could be considered irreparable injury as that term is used in the regulation, such injury alone is not sufficient to justify grant of a stay, regardless of how compelling the situation seems from the petitioner's perspective. Moreover, by logical inference, the injury to Abbott's potential competitors from granting the petition, should any applicaitons qualify for approval, represents an economic loss essentially comparable to that which Abbott alleges it will suffer if its stay is not granted.

The petition states that it is not frivolous and is being pursued in good faith. While we do not question your good faith in filing this petition, we do believe that its legal and scientific arguments are without merit. Moreover, Abbott has been on notice that it did not qualify for ten-year exclusivity since about February, 1985 when the agency issued its January, 1985 supplement to the *Approved Drug Products* publication announcing the agency's determination that Depakote was entitled only to two years of exclusivity. The firm waited until July 10, 1986, however, to dispute the agency's determination, and until August 29, 1986, less than a month before approvals of generics would be allowed, to submit this petition. However, we find it unnecessary to determine whether

the petition might be considered "frivolous" within the meaning of the regulation, inasmuch as the other criteria under which a stay is required have not been met.

The petition also maintains that there are sound public policy grounds supporting the stay, and that the delay resulting from the stay would not be outweighed by public health or other public interests. In support, the petition cites possible health consequences to patients who might be "lured to switch to a generic" version of Depakote (and then switched back again should Depakote's argument for ten-year market exclusivity be accepted). The petition also cites administrative efficiencies in that time and effort spent preparing and reviewing applications for generic versions of Depakote would not be wasted if a stay were in effect.

We do not believe that adverse public health consequences would result from approval of generic copies of Depakote. Patients would be protected because any generic copy of Depakote approved by FDA will have to meet the same standards for safety, strength, purity and effectiveness and will have to demonstrate bioequivalence to Depakote. Moreover, we believe that public policy favoring approval and marketing of generic products meeting the standards for approval is clearly expressed in the 1984 Amendments to the Act. As previously explained, FDA finds that it is not in the public interest to permit filing of a petition by a party to delay a required approval of a competitor's product. Therefore, the agency concludes that the policies cited in support of a stay are outweighed by other public interests.

In conclusion, for the reasons explained above, we find that the citizen petition has not shown that Depakote qualifies for ten years of exclusivity, nor has it been demonstrated that adequate grounds exist for the re-

quested stay of approval. We therefore deny both the citizen petition and the petition for stay.

Sincerely yours,

/s/ John M. Taylor
JOHN M. TAYLOR
Associate Commissioner
for Regulatory Affairs

Attachments

ATTACHMENT A

Exclusively Provisions in Section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act

general exclusivity provisions		"window" * exclusivity provisions	
D(ii):	for a drug, no active ingredient (including a salt or ester of the ingredient) of which has previously been approved: *5 years exclusivity* from date of approval	D(i):	same circumstances as D(ii), but approval was during the "window period": *10 years exclusivity* from date of approval
D(iii):	for a drug which includes an active ingredient (including a salt or ester of the active ingredient) previously approved—and whose application contains reports of new clinical investigations conducted or sponsored by applicant: *3 years exclusivity* from date of approval	D(v):	approval during "window" in circumstances similar, but broader, than those in (iii) and (iv)—as application or supplement need not have contained new clinical investigations: *2 years exclusivity* from enactment of the statute (i.e. until 9/24/86)
D(iv):	for a change (e.g. new indication) in a supplement that contains new clinical investigations conducted or sponsored by the person submitting the supplement: *3 years exclusivity* from date of approval, for the change		

* January 1, 1982-September 24, 1984.

Prepared by:HFN-362:CKimbrough:jmb:9/24/86:1p:
10/2/86:jmb:10/6/86:
Revised to incorporate comments:CKimbrough:12/23/86:
1p; revised by
CKimbrough 12/30/86:pg CKimbrough:1/2/87:jmb
CKimbrough:4/17/87:jmb
revised to incorporate comments from AWitt, SBlum, and
affidavit of
RWood:jmb:5/28/87 CKimbrough to incorporate
comments from
AWitt:jmb:7/15/87 CKimbrough:jmb:7/23/87:jmb:
8/6/87
CKimbrough & AWitt:jmb:9/24/87:CKimbrough &
AWitt:12/8/87:jmb:12/18/87
AWitt:jmb1/29/88

cc:
HFA-224
HFC-1
HFY-1/CKimbrough
HFN-1
HFN-120/PLeber, SBlum
HFN-201/Morrison
HFN-203/EDutra
GCF-1/AWitt
HFA-305/Docket Nos. 86P-0367/CP
86P-0367/PSA
HFN-300/DMichels
HFN-360
HFN-360/RF
HFN-360/CF
HFN-362/Paquin
0237K

ATTACHMENT B

AFFIDAVIT OF ROBERT H. WOOD, Ph.D.

ROBERT H. WOOD, Ph.D. declares and states as follows:

1. I am a Professor of Chemistry at the University of Delaware. I received a B.Sc. from the California Institute of Technology in 1953 and a Ph.D. from the University of California at Berkeley in 1957. My area of specialization is high temperature solution thermodynamics. A list of the articles I have published and the papers I have presented at scientific meetings is attached to my Curriculum Vitae.

2. I was asked by the Food and Drug Administration for my opinion on whether the active ingredient in the drug Depakote is a salt of valproic acid. Having reviewed the materials provided to me, which I understand include all of Abbott Laboratories' submissions to Docket No. 86P-0367, I have concluded that the compound in question is a salt of valproic acid.

3. The problem is one of nomenclature. The question is thus whether under the official rules for naming chemical entities, it is appropriate to call this compound a salt of valproic acid. The official source of nomenclature for chemical compounds is the International Union of Pure and Applied Chemistry (IUPAC) Rules for Nomenclature. The Rules for Nomenclature of Organic Compounds are not very detailed, but the Rules of Nomenclature for Inorganic Compounds, which are compatible with the rules for organic compounds, provide additional details and examples.

4. The rules for naming salts are found in § 6 of the rules for inorganic compounds. Section 6.2 ("Salts Containing Acid Hydrogen ("Acid" Salts)") and 6.3 ("Double Salts, Triple Salts, etc.") apply to the compound

at issue, whose empirical formula is $C_{16}H_{31}NaO_4$. All of the evidence submitted by Abbott indicates that it contains a sodium ion, a replaceable hydrogen combined with a valproate anion, and a valproate anion and that these species are held together by ionic bands and hydrogen bands and Van der Waals forces. This composition is the only one permitted, in light of the method by which the compound is synthesized (no carbon-carbon (covalent) bonds are formed) and the evidence of its structure (one replaceable hydrogen, two carboxylate functions, and no hydroxyl or keto groups). Under § 6.2, a compound containing replaceable acidic hydrogen, like the one at issue here, is considered an "acid salt," whose name is formed, in part, by adding the word "hydrogen" in front of the anion. Section 6.2 clearly states that "acid salts" are salts; an acid salt is simply a subcategory of "salt."

5. Sections 6.324 and 6.34 state that an acidic hydrogen is cited together with the anion to which it is bound and that the "stoichiometric" method is most practical for indicating the proportions of the constituents of the entity. The "stoichiometric" method describes the number or ratio of the cations to the anions. Here, there are two valporate anions to one sodium cation. Therefore, under these rules, the compound at issue should be called either sodium hydrogen bisvalproate, or sodium hydrogen divalproate.

6. It is important to note that the term "divalproate" in the name indicates only the stoichiometry; that is, the number of valporate anions. It does not indicate the existence of an entity called "divalproic acid." The use of the prefix "di" is simply a method of counting the number of valporate units, regardless of whether or how those valporate units are bound together. For example, the IUPAC rules cite the compound "hexasodium chloride flouride bissulphate." That name indicates that the compound is a salt containing two sulfates, *not* that it is a salt of bissulphuric acid; "bissulphuric acid" is unknown,

just as "divalproic acid" is unknown. Thus, the name "sodium hydrogen divalporate" shows that the compound is an acid salt of valproic acid, not of "divalproic acid."

7. The name "sodium hydrogen divalproate" is also the name applied by the Chemical Abstract Service (CAS) to this compound. CAS is unbiased and skilled in the art of naming compounds and has concluded that the compound at issue is appropriately named as a salt of valproic acid.

8. The rules for classifying and naming compounds that I have described were also used by Abbott itself in naming a related compound, as reflected in its U.S. Patent No. 4,598,070. In that patent, Abbott refers to a compound containing a metal, three replaceable hydrogens, and four valproate groups ("potassium trihydrogen tetravalproic acid") as an "acid salt of valproic acid." The change in stoichiometry from "sodium hydrogen divalproic acid" to "potassium trihydrogen tetravalproic acid" changes the chemical and physical properties of the compound, but not the way the salt is named. Nor does the name show that potassium trihydrogen tetravalproic acid is a salt of "tetravalproic acid;" "tetravalproic acid" like "divalproic acid" is not known to exist.

9. Abbott has argued that because of differences in hydrogen bonding or ionic coordination, this compound should not be considered a salt of valproic acid. Differences in hydrogen bonding and ionic coordination do not invalidate the name sodium hydrogen divalproate. Only differences in covalent bonds would invalidate the name, and Abbott has made no claim of a change in covalent bonding. If the single crystal x-ray structure of the compound were known, it is conceivable that an alternate and equally valid name as a coordinate compound of the sodium ion (IUPAC Rule 7) could be devised. Such a name would describe in detail the coordination of the sodium ion to the valproate and valproic acid liquids. This name would not, however, invalidate the name

sodium hydrogen divalproate. It would be a very unusual name since compounds of the sodium ion are not normally named this way (no examples come to mind), the name would be very complex (simpler names are to be preferred) and I know of no examples where similar compounds have been named in this manner.

10. Nor does any of the other evidence Abbott submitted change the nature of the compound as a salt of valproic acid. Abbott states that the compound is not a salt because of its high molecular weight when dissolved in tetrahydrofuran. However, its weight when dissolved in a solvent is irrelevant because hydrogen-bonded species can dissolve as monomers (low molecular weight) or as oligomers (high molecular weight), depending on the solvent used. The molecular weight as determined in any particular solvent is therefore irrelevant to the nomenclature for a compound. For instance, N-methylacetamide, a simple compound, dissolves in carbon tetrachloride as an oligomer with perhaps 10 units (i.e., a "ten-mer"), and in water as the monomer (single unit). Compounds are named according to their most simple structures; they are not considered polymers simply because they happen to dissolve as oligomers in a particular solvent.

11. The fact that sodium hydrogen divalproate may be an oligomeric complex does not mean that it is not a salt. As noted above, its oligomeric structure would be the result of hydrogen bonds, not covalent bonds. Valproic acid itself, in its crystal structure, undoubtedly forms hydrogen bonds with other units of valproic acid. Despite that hydrogen-bonded structure, it is still appropriately called valproic acid, not "divalproic" or "trivalproic" acid. Various examples demonstrate the irrelevance of hydrogen bonds to appropriate nomenclature. For instance, water is appropriately denoted as H_2O, not for instance $H_{10}O_5$, despite its supramolecular structure. Similarly, sodium chloride (table salt), in its normal crystalline form, is named sodium chloride

(NaCl) not tetrasodium tetrachloride (Na_4Cl_4); the simplest formula is always chosen. The appropriate name of the active ingredient in Depakote comes from the simplest formula of the compound, and is independent of hydrogen bonds. Thus sodium hydrogen divalproate is a salt of valproic acid, despite its possible oligomeric structure and the presence of more than one valproate unit in the compound.

12. The Fast Atom Bombardment Mass Spectrometry (FABMS) results of Abbott show that fast atoms produce oligomeric species in the gas phase. Since no claim is made for a covalent bonding pattern different from that implied by the name sodium hydrogen divalproate, this evidence is irrelevant. Oligomeric species in the gas phase held together by ionic and hydrogen bands are perfectly compatible with the name sodium hydrogen divalproate. It seems to me quite probable that other salts of organic acids would produce the same kinds of oligomeric species under this treatment. Perhaps even sodium valproate will produce this kind of oligomeric species, but this would not affect its status as a salt of valproic acid.

13. The solubility of sodium hydrogen divalproate in non-polar solvents is also not relevant to the issue of whether the compound is a salt. Although not typical, salts are known that are soluble in relatively non-polar solvents. An example of these are the tetraalkylammonium nitrates and picrates which dissolve in a variety of relatively non-polar solvents. For instance, conductances of many of these salts in ethylene chloride are reported by Harned and Owen (*"The Physical Chemistry of Eletrolytic Solutions, ACS Monograph* Series No. 137, 3rd ed. N.Y.: Reinhold, 1958, p. 703.)

14. The low melting point of the compound is also irrelevant because there are known examples of salts that melt near 25°C. For example, ethylammonium nitrate is liquid to 12°C (D.F. Evans, S-H Chen, G.W.

Schriver and E.M. Arnett, *Journal American Chemical Society* 103, 481 (1981).) The fact that many salts melt at higher temperatures does not mean that a compound with a lower melting point is not appropriately called a salt.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on June 30, 1987.

/s/ Robert H. Wood
ROBERT H. WOOD, Ph.D.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 88-5260

ABBOTT LABORATORIES,
Appellant

v.

FRANK D. YOUNG, DR., Commissioner,
Food and Drug Administration
and Consolidated Case No. 89-5183

Before: Mikva, Chief Judge; Edwards and Silberman, Circuit Judges

ORDER

[Filed Mar. 14, 1991]

Upon consideration of appellant's petition for rehearing, filed January 22, 1991, and of the response thereto, it is

ORDERED, by the Court, that the petition is denied.

Per Curiam
FOR THE COURT:
CONSTANCE L. DUPRE
Clerk

By: /s/ Robert A. Bonner
ROBERT A. BONNER
Deputy Clerk

Circuit Judge Edwards would grant the Petition for Rehearing.

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 88-5260

ABBOTT LABORATORIES,
Appellant

v.

FRANK D. YOUNG, DR., Commissioner,
Food and Drug Administration
and Consolidated Case No. 89-5183

Before: Mikva, Chief Judge; Wald, Edwards, Ruth B. Ginsburg, Silberman, Buckley, Williams, D. H. Ginsburg, Sentelle, Thomas, Henderson and Randolph, Circuit Judges

ORDER

[Filed Mar. 14, 1991]

Appellant's Suggestion For Rehearing *En Banc* has been circulated to the full Court. No member of the Court requested the taking of a vote thereon. Upon consideration of the foregoing it is

ORDERED, by the Court *en banc*, that the suggestion is denied.

Per Curiam
FOR THE COURT:
CONSTANCE L. DUPRE
Clerk

By: /s/ Robert A. Bonner
ROBERT A. BONNER
Deputy Clerk

APPENDIX D

THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, AS AMENDED BY THE HATCH-WAXMAN AMENDMENTS OF 1984

1. a. Ten-Year Market Exclusivity Applicable To Abbreviated New Drug Applications ("ANDAs")

Section 505(j)(4)(D)(i) of the Act, 21 U.S.C. § 355 (j)(4)(D)(i):

> If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on [September 24, 1984], the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b).

b. Ten-Year Market Exclusivity Applicable to "Paper" NDAs

Section 505(c)(3)(D)(i) of the Act, 21 U.S.C. § 355 (c)(3)(D)(i):

> If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on [September 24, 1984], the Secretary may not make the approval of another application for a drug for which the investigations

described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b).

2. a. Two-Year Market Exclusivity Applicable To ANDAs

Section 505(j)(4)(D)(v) of the Act, 21 U.S.C. § 355 (j)(4)(D)(v):

> If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982, and ending on [September 24, 1984], the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from [September 24, 1984].

b. Two-Year Market Exclusivity Applicable To "Paper" NDAs

Section 505(c)(3)(D)(v) of the Act, 21 U.S.C. § 355 (c)(3)(D)(v):

> If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was ap-

proved during the period beginning January 1, 1982, and ending on [September 24, 1984], the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from [September 24, 1984].

3. a. Five-Year Market Exclusivity Applicable to ANDAs Section 505(j)(4)(D)(ii) of the Act, 21 U.S.C. § 355 (j)(4)(D)(ii):

If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this subsection, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months

after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

b. Five-Year Market Exclusivity Applicable to "Paper" NDAs

Section 505(c)(3)(D)(ii) of the Act, 21 U.S.C. § 355 (c)(3)(D)(ii):

> If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this clause, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under subsection (b) after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A). The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight

months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven ane one-half years to have elapsed from the date of approval of the subsection (b) application.

4. a. Three-Year Market Exclusivity Provision Applicable to ANDAs

Section 505(j)(4)(D)(iii) of the Act, 21 U.S.C. § 355 (j)(4)(D)(iii):

> If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of enactment of this subsection and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) for such drug.

b. Three-Year Market Exclusivity Provision Applicable to "Paper" NDAs

Section 505(c)(3)(D)(iii) of the Act, 21 U.S.C. § 355 (c)(3)(D)(iii):

> If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient)

that has been approved in another application approved under subsection (b), is approved after the date of the enactment of this clause and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

5. a. Three-Year Market Exclusivity For Supplemental NDAs Applicable to ANDAs

Section 505(j)(4)(D)(iv) of the Act, 21 U.S.C. § 355 (j)(4)(D)(iv):

If a supplement to an application approved under subsection (b) is approved after the date of enactment of this subsection and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

b. Three-Year Market Exclusivity For Supplemental NDAs Applicable to "Paper" NDAs

Section 505(c)(3)(D)(iv) of the Act, 21 U.S.C. § 355(c)(3)(D)(iv):

> If a supplement to an application approved under subsection (b) is approved after the date of enactment of this clause and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

6. Patent Term Extension

35 U.S.C. § 156(f)

> **§ 156. Extension of Patent Term**
>
> * * * *
>
> (f) For purposes of this section:
>
> (1) The term "product" means:
>
> (A) A drug product.
>
> (B) Any medical device, food additive, or color additive subject to regulation under the Federal Food, Drug, and Cosmetic Act.
>
> (2) The term "drug product" means the active ingredient of—

(A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act),

* * * *

including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.